corn starch, potato starch, alginic acid, a lubricant such as magnesium stearate; and a sweetening agent such as sucrose lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

For parenteral administration the disclosed positive allosteric modulators of mGluR2 can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically-acceptable salts of the compounds. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

In addition, to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation, for example, subcutaneously or intramuscularly or by intramuscular injection. Thus, for example, as an emulsion in an acceptable oil, or ion exchange resins, or as sparingly soluble derivatives, for example, as sparingly soluble salts.

Preferably disclosed positive allosteric modulators of mGluR2 or pharmaceutical formulations containing these compounds are in unit dosage form for administration to a mammal. The unit dosage form can be any unit dosage form known in the art including, for example, a capsule, an IV bag, a tablet, or a vial. The quantity of active ingredient in a unit dose of composition is an effective amount and may be varied according to the particular treatment involved. It may be appreciated that it may be necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration which may

be by a variety of routes including oral, aerosol, rectal, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal and intranasal.

PHARMACOLOGY

The compounds provided in this invention are positive allosteric modulators of metabotropic receptors, in particular they are positive allosteric modulators of mGluR2. The compounds of the present invention do not appear to bind to the glutamate recognition site, the orthosteric ligand site, but instead to an allosteric site within the seven transmembrane region of the receptor. In the presence of glutamate or an agonist of mGluR2, the compounds of this invention increase the mGluR2 response. The compounds provided in this invention are expected to have their effect at mGluR2 by virtue of their ability to increase the response of such receptors to glutamate or mGluR2 agonists, enhancing the response of the receptor. Hence, the present invention relates to a compound for use as a medicine, as well as to the use of a compound according to the invention or a pharmaceutical composition according to the invention for the manufacture of a medicament for treating or preventing a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR2 allosteric modulators, in particular positive mGluR2 allosteric modulators.

Also, the present invention relates to the use of a compound according to the invention or a pharmaceutical composition according to the invention for the manufacture of a medicament for treating, or preventing, ameliorating, controlling or reducing the risk of various neurological and psychiatric disorders associated with glutamate dysfunction in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR2 positive allosteric modulators.

Where the invention is said to relate to the use of a compound or composition according to the invention for the manufacture of a medicament for e.g. the treatment of a mammal, it is understood that such use is to be interpreted in certain jurisdictions as a method of e.g. treatment of a mammal, comprising administering to a mammal in need of such e.g. a treatment, an effective amount of a compound or composition according to the invention.

In particular, the neurological and psychiatric disorders associated with glutamate dysfunction, include one or more of the following conditions or diseases: acute neurological and psychiatric disorders such as cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, dementia (including AIDS-induced dementia), Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, ocular damage, retinopathy, cognitive disorders, idiopathic and drug-induced Parkinson's disease, muscular spasms and disorders associated with muscular spasticity including tremors, epilepsy, convulsions, migraine (including migraine headache), urinary incontinence, substance tolerance, substance withdrawal (including substances such as opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.), psychosis, schizophrenia, anxiety (including generalized anxiety disorder, panic disorder, and obsessive compulsive disorder), mood disorders (including depression, mania, bipolar disorders), trigeminal neuralgia, hearing loss, tinnitus, macular degeneration of the eye, emesis, brain edema, pain (including acute and chronic states, severe pain, intractable pain, neuropathic pain, and post-traumatic pain), tardive dyskinesia, sleep disorders (including narcolepsy), attention deficit/hyperactivity disorder, and conduct disorder.

In particular, the condition or disease is a central nervous system disorder selected from the group of anxiety disorders, psychotic disorders, personality disorders, substance-related disorders, eating disorders, mood disorders, migraine, epilepsy or convulsive disorders, childhood disorders, cognitive disorders, neurodegeneration, neurotoxicity and ischemia.

Preferably, the central nervous system disorder is an anxiety disorder, selected from the group of agoraphobia, generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder, posttraumatic stress disorder (PTSD), social phobia and other phobias.

Preferably, the central nervous system disorder is a psychotic disorder selected from the group of schizophrenia, delusional disorder, schizoaffective disorder, schizophreniform disorder and substance-induced psychotic disorder

Preferably, the central nervous system disorder is a personality disorder selected from the group of obsessive-compulsive personality disorder and schizoid, schizotypal disorder.

Preferably, the central nervous system disorder is a substance-related disorder selected from the group of alcohol abuse, alcohol dependence, alcohol withdrawal, alcohol withdrawal delirium, alcohol-induced psychotic disorder, amphetamine dependence, amphetamine withdrawal, cocaine dependence, cocaine withdrawal, nicotine dependence, nicotine withdrawal, opioid dependence and opioid withdrawal.

Preferably, the central nervous system disorder is an eating disorder selected from the group of anorexia nervosa and bulimia nervosa.

Preferably, the central nervous system disorder is a mood disorder selected from the group of bipolar disorders (I & II), cyclothymic disorder, depression, dysthymic disorder, major depressive disorder and substance-induced mood disorder.

Preferably, the central nervous system disorder is migraine.

Preferably, the central nervous system disorder is epilepsy or a convulsive disorder selected from the group of generalized nonconvulsive epilepsy, generalized convulsive epilepsy, petit mal status epilepticus, grand mal status epilepticus, partial epilepsy with or without impairment of consciousness, infantile spasms, epilepsy partialis continua, and other forms of epilepsy.

Preferably, the central nervous system disorder is attention-deficit/hyperactivity disorder.

Preferably, the central nervous system disorder is a cognitive disorder selected from the group of delirium, substance-induced persisting delirium, dementia, dementia due to HIV disease, dementia due to Huntington's disease, dementia due to Parkinson's disease, dementia of the Alzheimer's type, substance-induced persisting dementia and mild cognitive impairment.

Of the disorders mentioned above, the treatment of anxiety, schizophrenia, migraine, depression, and epilepsy are of particular importance.

At present, the fourth edition of the Diagnostic & Statistical Manual of Mental Disorders (DSM-IV) of the American Psychiatric Association provides a diagnostic

tool for the identification of the disorders described herein. The person skilled in the art will recognize that alternative nomenclatures, nosologies, and classification systems for neurological and psychiatric disorders described herein exist, and that these evolve with medical and scientific progresses.

Because such positive allosteric modulators of mGluR2, including compounds of Formula (I), enhance the response of mGluR2 to glutamate, it is an advantage that the present methods utilize endogenous glutamate.

Because positive allosteric modulators of mGluR2, including compounds of Formula (I), enhance the response of mGluR2 to agonists, it is understood that the present invention extends to the treatment of neurological and psychiatric disorders associated with glutamate dysfunction by administering an effective amount of a positive allosteric modulator of mGluR2, including compounds of Formula (I), in combination with an mGluR2 agonist.

The compounds of the present invention may be utilized in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which compounds of Formula (I) or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone.

METHODS OF SYNTHESIS

The compounds according to the invention, in particular the compounds according to the Formula (I), (II), (II-a), (II-b), (II-c), (II-c1), (II-c2), (II-c3), (III), (III-a), (III-b), (III-c), (III-c1), (III-c2), (III-c3), (IV), (V), (V-a) and (V-b), may be prepared by methods known in the art of organic synthesis or by the following synthesis schemes. In all of the schemes described below it is understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with the general principles of organic chemistry. Protecting groups are manipulated according to standard methods (T.W. Green and P.G.M. Wuts, **1991**, *Protecting Groups in Organic Synthesis*, John Wiley & Sons, Inc.). These groups are then removed at a convenient stage of the synthesis using methods that are readily apparent to those skilled in the art.

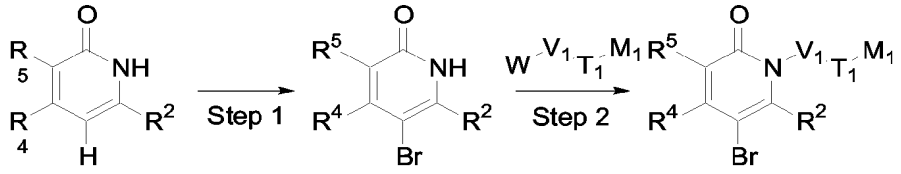
The compounds according to the invention may be represented as a mixture of enantiomers which may be resolved into their individual *R*- or *S*-enantiomers. If for instance, a particular enantiomer is required it may be prepared by asymmetric synthesis or by derivation with a chiral auxiliary and the resulting diastereomeric mixture separated. The auxiliary group can then be cleaved to provide the desired pure enantiomers. Alternatively, where the molecule contains a basic functional group such as an amino or an acidic functional group such as a carboxyl functional group, resolution may be performed by fractional crystallization from various solvents as the salt of an optical active acid or by other methods known in the literature (*e.g.* chiral column chromatography).

Resolution of the final product, an intermediate or a starting material may be performed by any suitable method known in the art (E.L. Eliel, S.H. Wilen and L.N. Mander, **1984**, *Stereochemistry of Organic Compounds*, Wiley-Interscience).

Many of the heterocyclic compounds of Formula (I) to (V-b) where M_1 or M_2 is a heteroaromatic or heterocyclic group may be prepared using synthetic routes well known in the art (A.R. Katrizky and C. W. Rees, **1984**, *Comprehensive Heterocyclic Chemistry*, Pergamon Press).

The synthesis of mGluR2 modulators disclosed herein are shown in the following synthetic schemes. Specific conditions for carrying out these reactions are provided in the examples. In one embodiment, the invention provides compounds of Formula V, where the $V_1T_1M_1$ group can be introduced by alkylation (N-C, bond formation) using the appropriate starting materials (*i.e.* pyridine derivatives or pyridinone derivatives). The $V_1T_1M_1$ group can be introduced by an alkylation (O-C or N-C, bond formation), a reductive amination (C-N, bond formation), or by displacement of a leaving group Cl, Br, I or OP, where OP is defined as a leaving group (*e.g.* tosylate, and mesylate) (C-N or C-O, bond formation). C-N, C-O and C-C bond formation are well understood by a person skilled in the art of organic chemistry. The synthetic schemes described below show exemplified approaches to compounds of the present invention but these routes should not be taken as the only possible synthetic routes to compounds of the present invention.

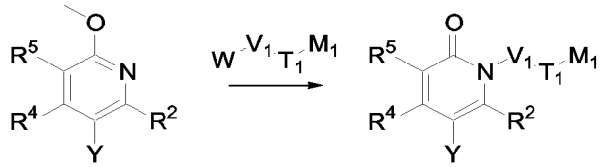
Pyridinones **g1** are commercially available or may be synthesized in ways described in the literature (Synthesis, 2002, 79-82; Tetrahedron Asymmetry, 1998, 2027; J. Heterocycl. Chem., 1974, 251; Synth. Commun., 1994, 1367). Selective bromination of a suitably substituted pyridine **g1** leads to bromopyridine **g2**. It is well known that such brominations can lead to isomers (Bioorg. Med. Chem. Lett., 2002, 197-202) which can be separated by crystallization or column chromatography. The group $V_1T_1M_1$ can then be introduced in one step by alkylation using an elaborated W-$V_1T_1M_1$ group (where W is Cl, Br or OP) or alternatively, a HO-$V_1T_1M_1$ group using Mitsunobu conditions (Tetrahedron Letters, 1994, 2819-2822). It is described in the literature that this procedure may give undesired O-alkylated product which can be separated by crystallization or column chromatography.



g1 **g2** **g3**

Scheme 1

Alternatively, the group $V_1T_1M_1$ can be introduced by reaction of a suitably substituted 2-methoxypyridine with an elaborated W-$V_1T_1M_1$ where W is Cl, Br or OP (Scheme 2).



g4 Y=Br,COOMe,CN,CHO **g5**

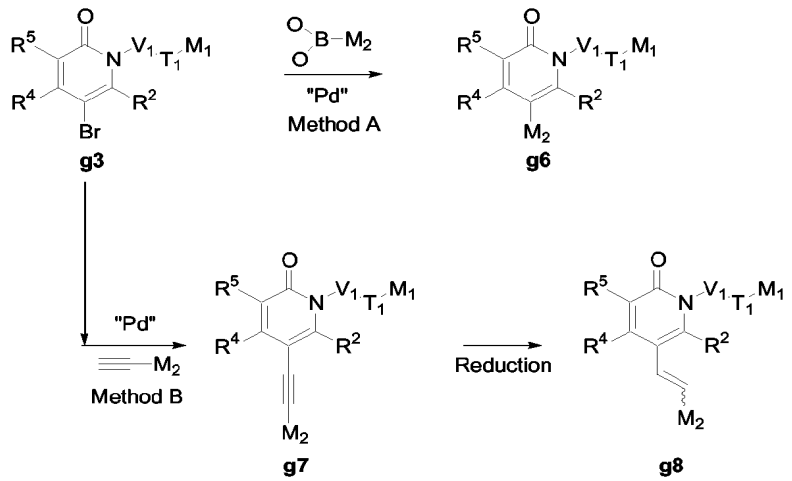
Scheme 2

Suitably substituted, means in the context of the invention, substituents as defined in the list of preferred substituents or substituent which can be precursor of the

aforementioned preferred substituents and are therefore protected in a manner that a person skilled in the art would recognize.

The introduction of the $V_2T_2M_2$ can be done through carbon-carbon bond formation (Scheme 3).

- Using a boronic acid under Suzuki-Miyaura conditions (Chem. Rev., 1995, 95, 54, 263) where V_2T_2 are bonds and M_2 is aryl, heteroaryl, cycloalkenearyl or cycloalkeneheteroaryl (Method A).
- Using a suitable alkylidinyl group under Sonogashira condition (J. Med. Chem., 2000, 43, 4288-4312) where V_2T_2 is an alkylidinyl group and M_2 is aryl, alkylaryl, heteroaryl or alkylheteroaryl (Method B).
- Using a suitable alkylidenyl group under Heck condition where V_2T_2 is alkylidenyl group and M_2 is aryl, alkylaryl, heteroaryl or alkylheteroaryl.



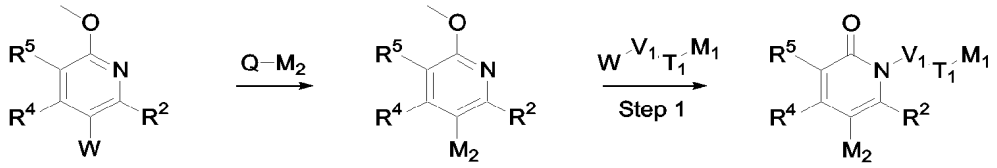
Scheme 3

The Suzuki-Miyaura (Method A, Scheme 3) carbon-carbon coupling reaction requires a catalyst such as $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $Pd_2(dppf)$ or $Pd(OAc)_2$ and an aqueous or non-aqueous base such as sodium carbonate, potassium carbonate, sodium hydroxide or cesium fluoride in a suitable solvent such as dioxane, toluene, dimethoxyethane or DMF. The Sonogashira (Method B, Scheme 3) carbon-carbon coupling reaction requires a catalyst such as $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$ or $Pd(OAc)_2$ in a suitable solvent such as DMF, acetonitrile or benzene. Typically, a co-catalyst such as

copper (I) iodide and a base such as triethylamine, diisopropylamine, or KOAc will also be present in the reaction mixture. The Suzuki-Miyaura and Sonogashira reactions typically react at temperatures ranging from 0°C to 150°C. Typically, the reaction is maintained for 1 to 24 hours, with 12 hours usually being sufficient. The product of the reaction can be isolated and purified using standard techniques such as solvent extraction, column chromatography, crystallization, distillation and sublimation.

For a person skilled in the art of organic chemistry it is well understood that compound **g7** can be hydrogenated under catalytic conditions using for example Pd/C and H_2 or ammonium formate (as hydrogen source) to afford the partially reduced analogs **g8** which are also part of this invention. It is noteworthy that a full hydrogenated version cannot be achieved under these conditions and therefore another approach should be envisaged to achieve fully reduced compounds (Scheme 8).

The inventors are aware that some chemical groups within $V_1T_1M_1$ may not be compatible with the aforementioned carbon-carbon bond forming reaction (*i.e.* Sonogashira, Heck or Suzuki-Miyaura). Therefore, the $V_1T_1M_1$ group can be introduced later in the synthesis (Scheme 4, Method A) and for example the Sonogashira reaction could be performed in the first step on a suitably substituted 2-methoxypyridine 5-boronic acid **g9**. The synthesis of such boronic acid is well described in the literature (J. Org. Chem., 2002, 67, 7541-7543) from commercial precursors with aryl and heteroaryl triflates or bromides. Aryl and heteroaryl bromides are available from commercial sources. The synthesis can also be performed from a suitably substituted 2-methoxypyridine having in position 5 an halide or a triflate reacting in a Suzuki-Miyaura reaction with a boronic compound Q-M_2 where Q is $B(OR)_2$. (Method B)

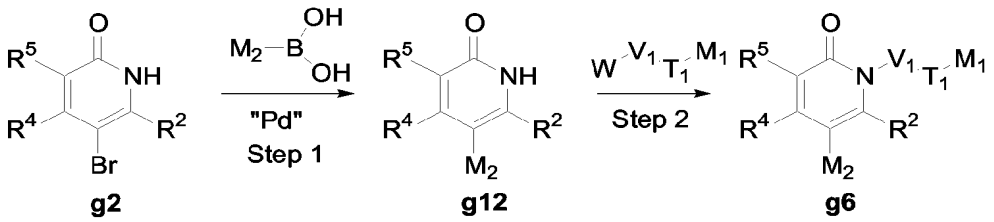


g9 **g10** **g11**

Method A: W=$B(OR)_2$, Q=OSO_2CF_3, Br
Method B: W=OSO_2CF_3, Br, Q=$B(OR)_2$

Scheme 4

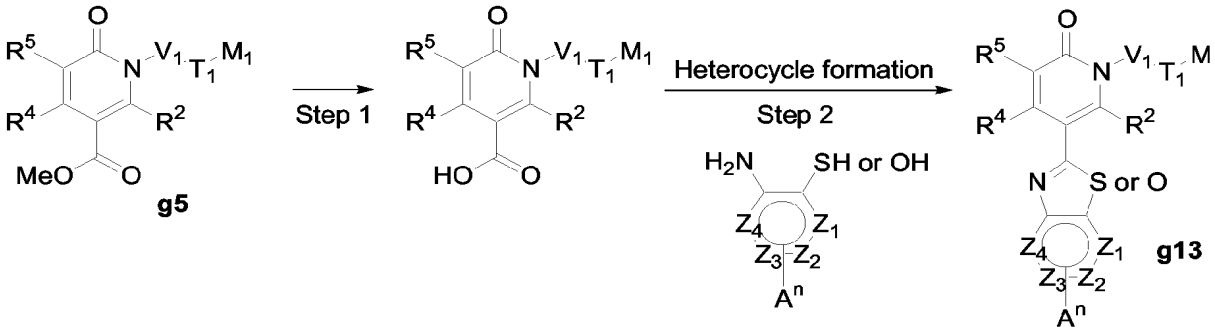
Likewise, the $V_2T_2M_2$ (in this case V_2 and T_2 are bonds and M_2 is aryl, alkenearyl, aryl or heteroaryl) group can be introduced onto **g2** in the first step (Scheme 5), to yield compound **g12** which is then subjected to W-$V_1T_1M_1$ under conditions similar to those described in Scheme 1, Step 2.



g2 **g12** **g6**

Scheme 5

For a person skilled in the art of organic chemistry it is well understood that functionalities present in compound **g5** (where Y is COOMe, CN or CHO) may be further transformed into compound **g13** as exemplified where Y is COOMe (Scheme 6).

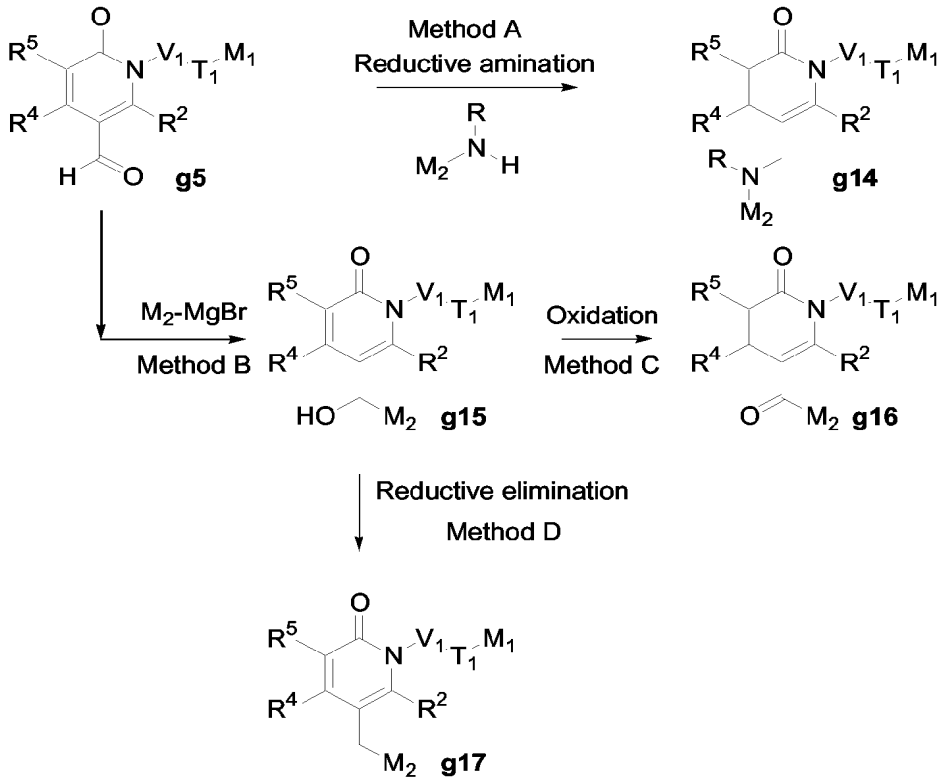


g5 **g13**

Scheme 6

The acid compound generated from the ester **g5** is an excellent anchoring point for heterocycle formation such as benzothiazole, oxadiazole, benzoxazole or isoxazole. The composition of the invention is not limited only to the aforementioned heterocycles but extends to our preferred list of heterocycles which may be synthesized through a similar scheme. (A. R. Katrizky and C. W. Rees, 1984, *Comprehensive Heterocyclic Chemistry*, Pergamon Press).

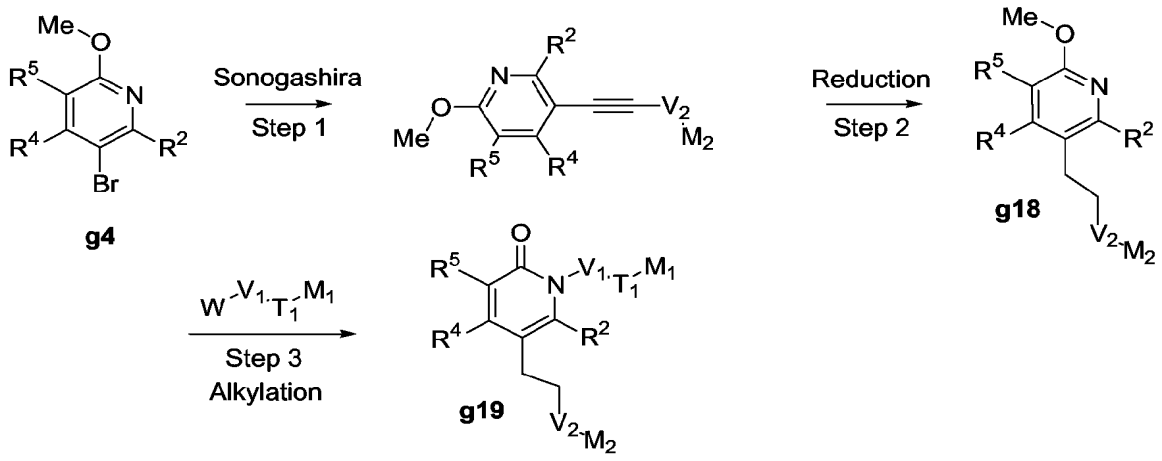
For one skilled in the art of organic chemistry it is well understood that functionalities present in compound **g5** (where Y is COOMe, CN or CHO) may be further transformed into compounds **g14**, **g15**, **g16** and **g17** (Scheme 7).



Scheme 7

The reductive amination to afford compound **g14** is well documented in the literature (Helv. Chim. Acta, 1998, 81, 1754). The synthesis of alcohol **g15** may utilize organometallic reagents such as the Grignard reagent exemplified here. However, many alternative organometallic reagents may be used and their preparation and use is well exemplified in the literature (M. Schlosser, 1994, *Organometallics in Synthesis*, John Wiley & Sons, Inc.). Compound **g15** can be subsequently transformed into ketone **g16** *via* oxidation or into alkyl **g17** *via* reductive elimination.

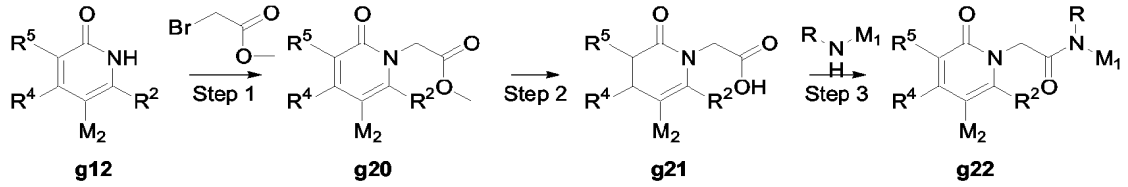
The inventors are aware that for specific compounds of the invention for instance compound **g19** neither compound **g5** nor compound **g3** are compatible intermediates, therefore, compound **g4** would be a suitable starting material (Scheme 8).



Scheme 8

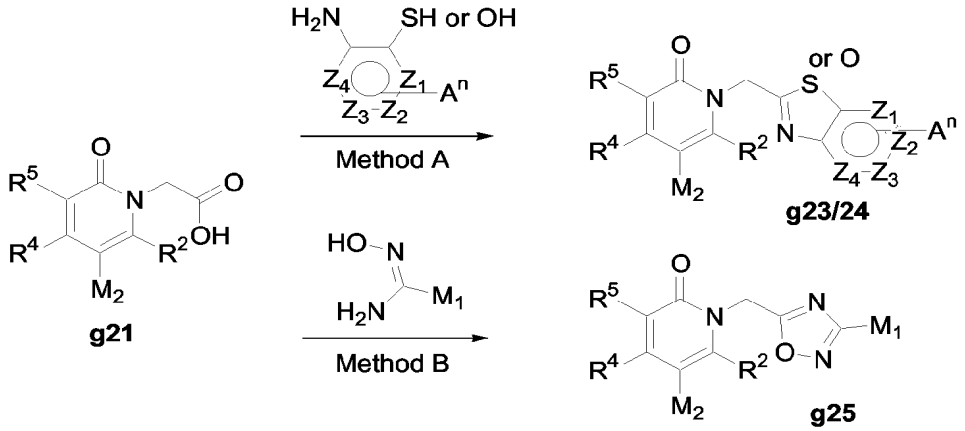
All the methods used in Scheme 8 have been described in previous schemes.

A person skilled in the art of organic chemistry would recognise that the $V_1T_1M_1$ group assembly may be constructed stepwise to afford compounds **g20** and **g22** (Scheme 9).



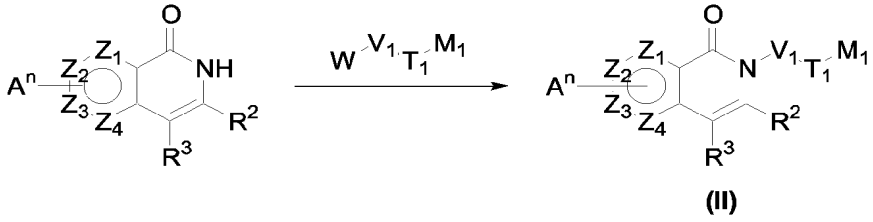
Scheme 9

The acid moiety present in **g21** is an excellent anchoring point for heterocycle formation such as benzothiazole **g23**, benzoxazole **g24**, oxadiazole **g25** and isoxazole (Scheme 10) which are also compounds of this invention. The composition of the invention is not limited only to the aforementioned heterocycles but extend to our preferred list of heterocycles which can be synthesized through a similar scheme (A. R. Katrizky and C. W. Rees, 1984, *Comprehensive Heterocyclic Chemistry*, Pergamon Press; Chem. Pharm. Bull., 1999, 47, 120–122).



Scheme 10

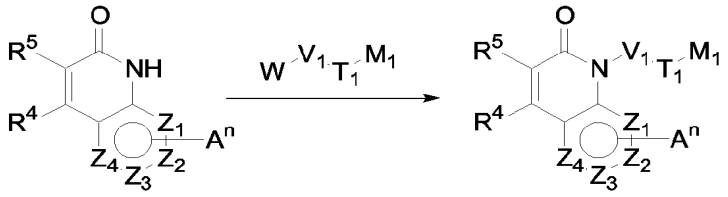
In another embodiment, the invention provides compounds of Formula (II) (Scheme 11). The synthesis of starting materials (*i.e.* isoquinolin-1-one derivatives) when not commercially available are well described in the literature (Chem. Ber., 1972, 3726-3747; Chem. Pharm. Bull., 1982, 1680-1691, Chem. Pharm. Bull., 1986, 2754-2759). For a person skilled in the art of organic chemistry it is well understood that the preferred substituents as defined in the claims can be introduced using similar chemistry. $V_1T_1M_1$ may be introduced using an elaborated W-$V_1T_1M_1$ (where W is Cl, Br or OP) in the presence of base such as NaH, K_2CO_3 or NaHMDS in a suitable solvent such as THF or DMF. It is noteworthy that these procedures may lead to undesired O-alkylated product which can be separated by crystallization or column chromatography.



Scheme 11

In another embodiment, the invention provides compounds of Formula (III) (Scheme 12). The syntheses of similar compounds are well described in the literature (Magn. Reson. Chem., 26, 1988, 511-517; J. Chem. Soc. Perkin Trans., 1, 1980, 197-202; J. Heterocycl. Chem., 1983, 1707-1708, Heterocycles, 1997, 483-492). For a person

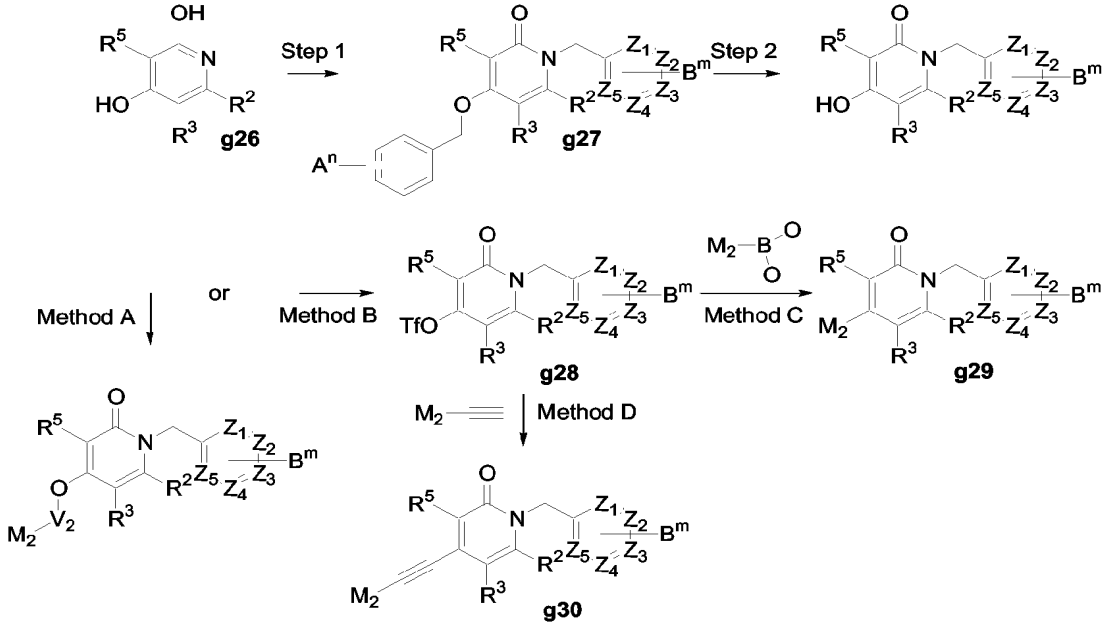
skilled in the art of organic chemistry it is well understood that preferred substituents as defined in the claims can be introduced using similar chemistry. $V_1T_1M_1$ can be introduced using an elaborated W-$V_1T_1M_1$ (where W is Cl, Br or OP) in presence of base such as NaH or K_2CO_3 or alternatively, with HO-$V_1T_1M_1$ using Mitsunobu condition (Tetrahedron Letters, 1994, 2819-2822) It is noteworthy that this procedure may lead to undesired O-alkylated product which can be separated by crystallization or column chromatography.



(III)

Scheme 12

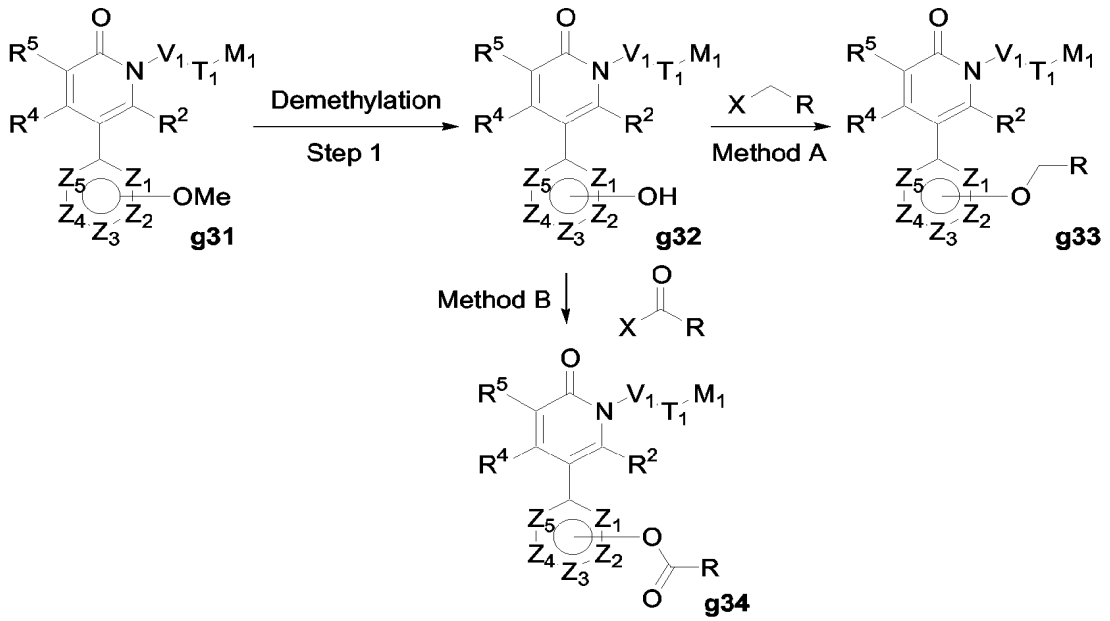
In another embodiment of the invention provides compounds of Formula (IV) (Scheme 13).



Scheme 13

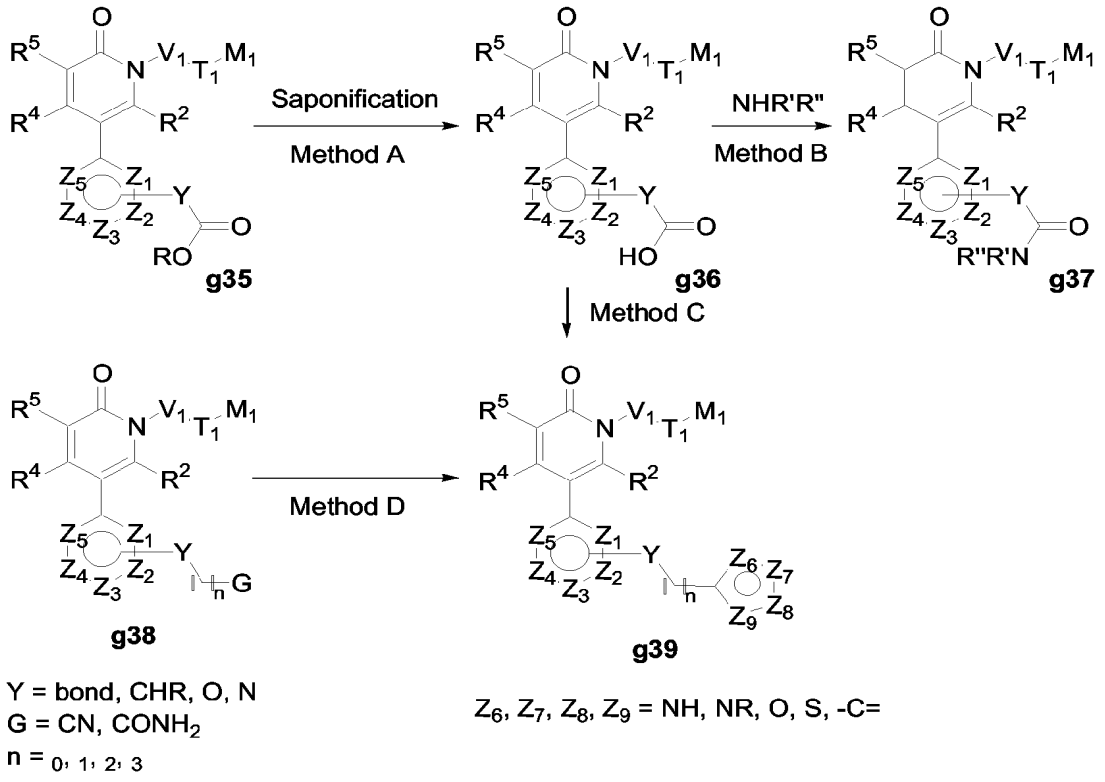
Alkylation of 2,4-dihydroxypyridine (commercially available) with a substituted benzyl halide is achieved using a base such as K_2CO_3 in a suitable solvent such as THF, CH_3CN or DMF under heating at 80°C. This transformation may lead to a mixture of products which can then be separated to isolate intermediate **g27**. The deprotection of the hydroxybenzyl moiety can be selectively achieved using Pd/C and H_2 or ammonium formate (as hydrogen source). The subsequent alcohol can either be alkylated as described previously or transformed into a triflate. Triflate **g28** is a rather sensitive molecule and is used in the carbon-carbon bond formation (exemplified here with a Suzuki-Miyaura reaction or Sonogashira coupling, Scheme 3).

In another embodiment of the present invention compounds of Formula (V) may be prepared in accordance with Scheme 14. Compound **g31** can be deprotected in the presence of BBr_3 (J. Med. Chem., 1997, 40, 2085-2101). The resulting alcohol **g32** can be alkylated by XCH_2R where X may be a good leaving group such as Cl, Br, I or OP in the presence of a base such as K_2CO_3, Cs_2CO_3 or NaH in a suitable solvent such as DMF, acetone or tetrahydrofuran at an appropriate temperature or acylated by XCOR where X is Cl in the presence of a base such as Et_3N or DIEA in a suitable solvent.



Scheme 14

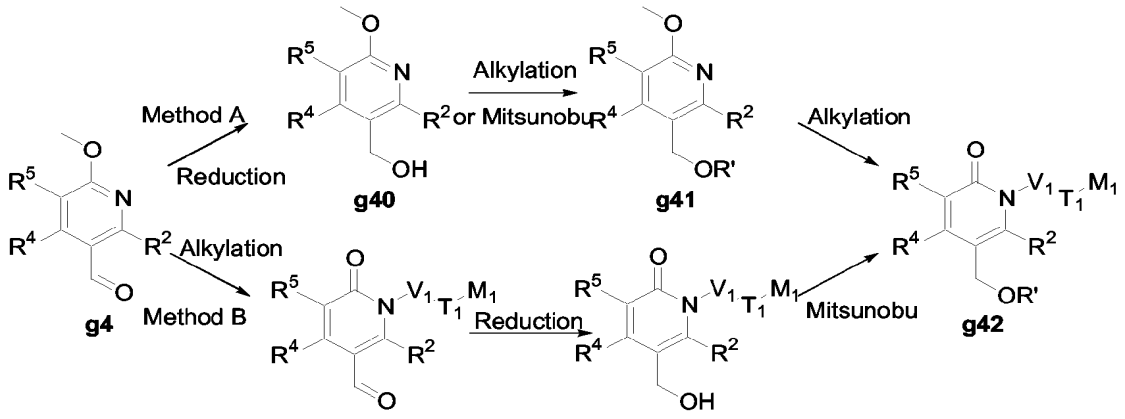
In another embodiment of the present invention, the compounds of Formula (V) may be prepared according to the synthetic sequences illustrated in Scheme 15. Compound **g35** may be hydrolyzed by standard procedures followed by reaction with a primary or secondary amine in order to lead to compound **g37** (Scheme 6). Compounds **g36** and **g38** represent an excellent anchoring point (acid, nitrile or amide) for heterocycle formation such as thiazole, oxadiazole, oxazole or isoxazole. The composition of the invention is not limited only to the aforementioned heterocycles but extends to our preferred list of heterocycles which can be synthesized through a similar scheme (A. R. Katrizky and C. W. Rees, 1984, *Comprehensive Heterocyclic Chemistry*, Pergamon Press).



Scheme 15

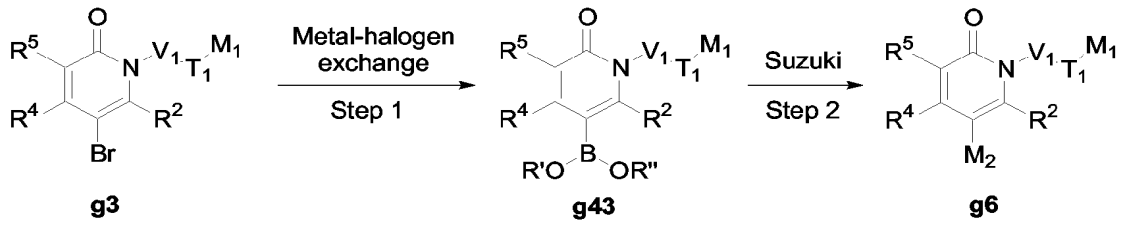
In another embodiment of the present invention, compounds of Formula (V) may be prepared in accordance with Scheme 16. For a person skilled in the art of organic chemistry it is well understood that aldehyde **g4** can be reduced using $LiAlH_4$ to afford the alcohol **g40** which can be alkylated using either R'X (where X is Cl, Br or OP) in

the presence of a base such as K_2CO_3, Cs_2CO_3 or NaH in a suitable solvent such as DMF, acetone or tetrahydrofuran or alternatively, using R'OH with Mitsunobu conditions as described in Scheme 1. Another way to synthesize compound **g42** is to first alkylate compound **g4** then reduce and finally to alkylate a second time.



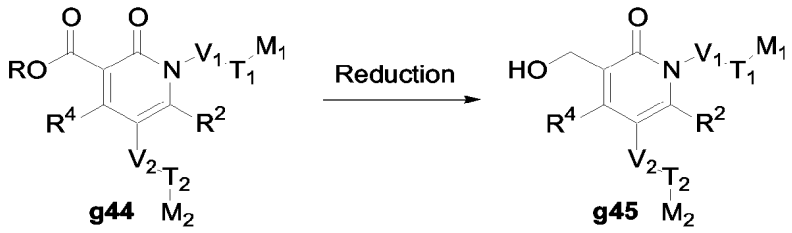
Scheme 16

In one embodiment of the present invention compounds of Formula (V-b) may be prepared according to the synthetic sequences illustrated in Scheme 17. Compound **g3** can be transformed into boronic esters via metal-halogen exchange in the presence of $Pd(PPh_3)_4$. The resulting boronic esters can be coupled to M_2 via Suzuki-Miyaura coupling as described in Scheme 3.



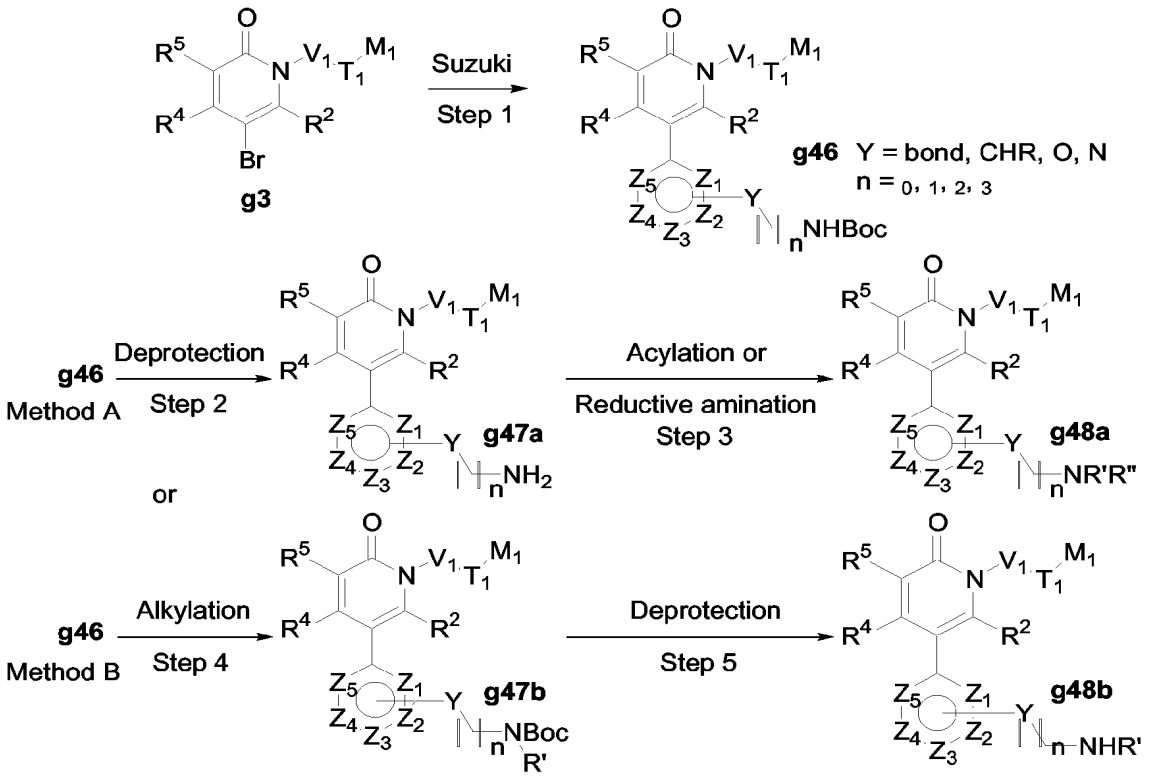
Scheme 17

In another embodiment of the present invention, compounds of Formula (V) may be prepared in accordance with Scheme 18. For one skilled in the art of organic chemistry it is well understood that ester **g44** can be reduced using $LiAlH_4$ to afford the alcohol **g45**.



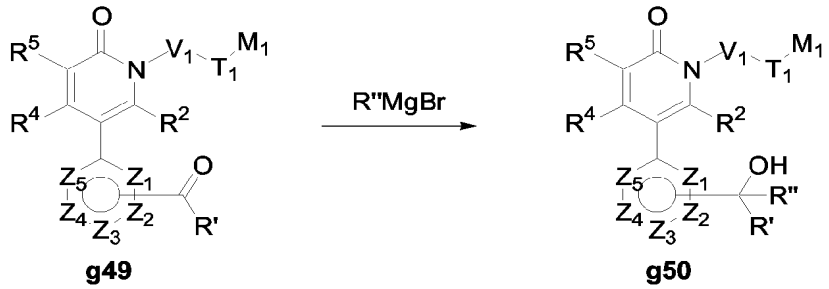
Scheme 18

In another embodiment of the present invention, the compounds of Formula (V) may be also prepared according to the synthetic sequences illustrated in Scheme 19. Compound **g3** can be submitted to Suzuki-Miyaura coupling with boronic compounds being substituted by a protected amino moiety. Then in Method A, the removal of the Boc group in compound **g46** may be achieved under classical conditions well known in the art such as HCl or TFA. The resulting primary amine can then be either acylated by standard procedure or submitted to reductive amination (Scheme 7). And in Method B, compound **g46** can be submitted first to alkylation using preferentially NaH as base and tetrahydrofurane as organic solvent followed by deprotection under acidic conditions (for example the reaction can be done in an organic solvent such as DCM with an acid such as TFA typically at room temperature to give compound **g48b**.



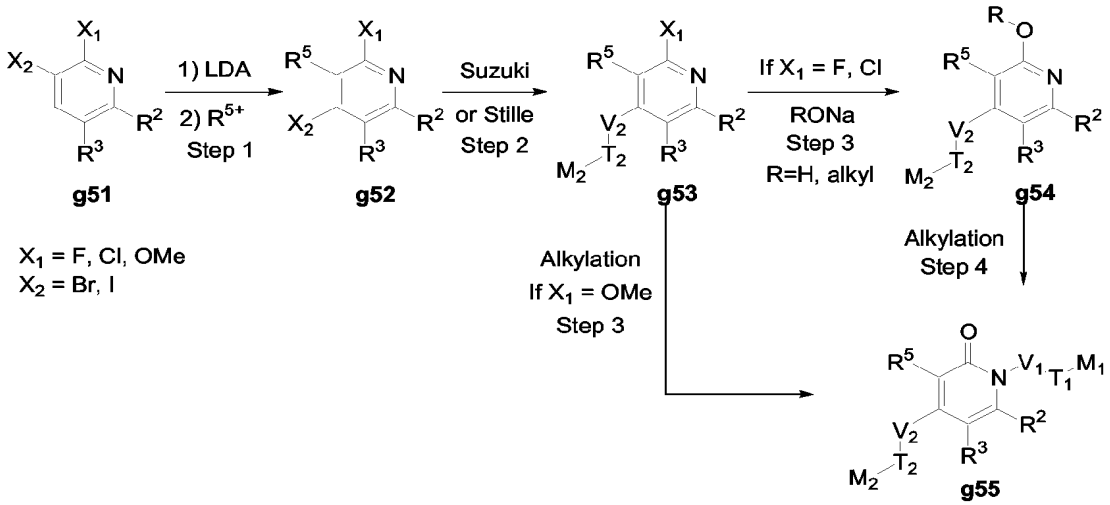
Scheme 19

The synthesis of alcohol **g50** may requires organometallic reagents such as the Grignard reagent exemplified here (Scheme 20). However, many alternative organometallic reagents may be used and their preparation and use is well exemplified in the literature (M. Schlosser, 1994, *Organometallics in Synthesis*, John Wiley & Sons, Inc.).



Scheme 20

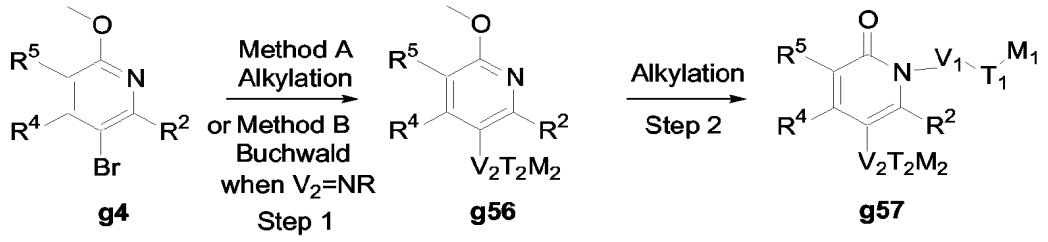
Another embodiment of the invention provides compounds of Formula (IV) (exemplified in Scheme 21). Substituted 3-bromo-pyridine or 3-iodopyridine **g51** can be subjected to directed ortho metalation at low temperatures (*e.g.* -78°C) in a solvent such as. THF or diethyl ether with lithium diisopropylamide and subsequently quenched with an electrophilic halogen source (*e.g.* Br_2 or I_2). 4-halopyridine **g52** can then be functionalized by carbon-carbon bond forming reaction (Step 2, exemplified here by Suzuki-Miyaura or Stille reaction) under condition similar to those described in Scheme 3. Displacement of 2-halopyridine **g53** by sodium methoxide in methanol yielded 2-methoxypyridine **g54**. Subsequent alkylation was then performed as described in Scheme 2 to yield pyridinone **g55**.



Scheme 21

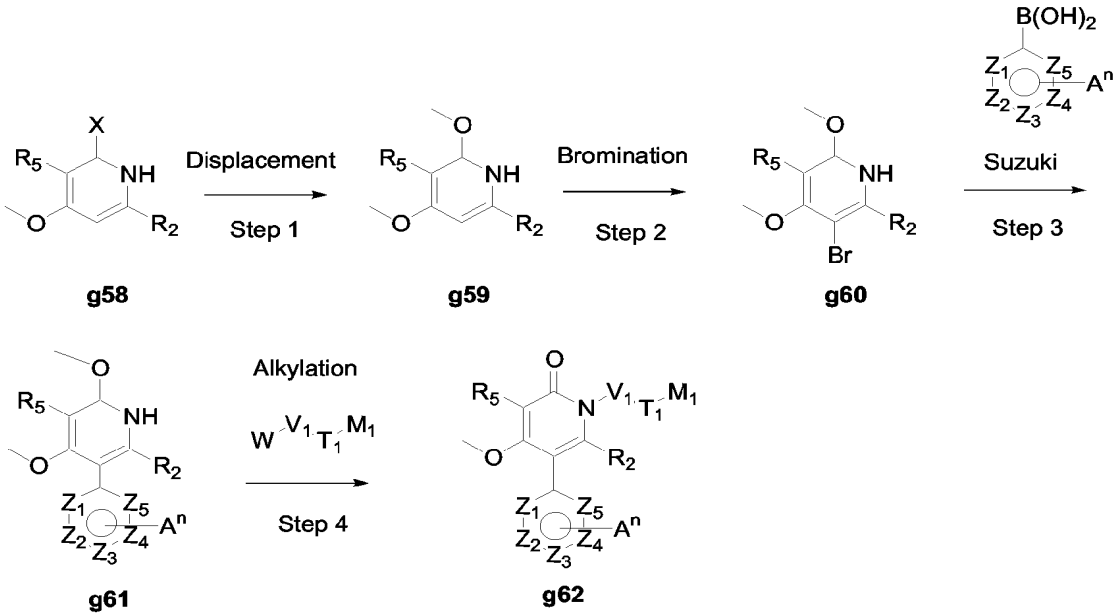
Another embodiment of the invention provides compounds of Formula (V) (exemplified in Scheme 22). Method A, substituted 5-bromo-2-methoxy-pyridine **g4** was subjected to lithium-halogen exchange at -78°C in an a solvent such as THF or diethyl ether with butyl lithium and quenched with a substituted alkyl bromide ($M_2V_2T_2X$) to give compound **g56**. Alkylation was then performed as described in example 1 to give compound **g57**.

In a similar manner, compound **g4** can be involved in a Buchwald reaction (Method B) with an amine in conditions known in the art using palladium, a suitable catalyst and a ligand to afford after alkylation compound **g57** (where V_2 = NH or N-alkyl).



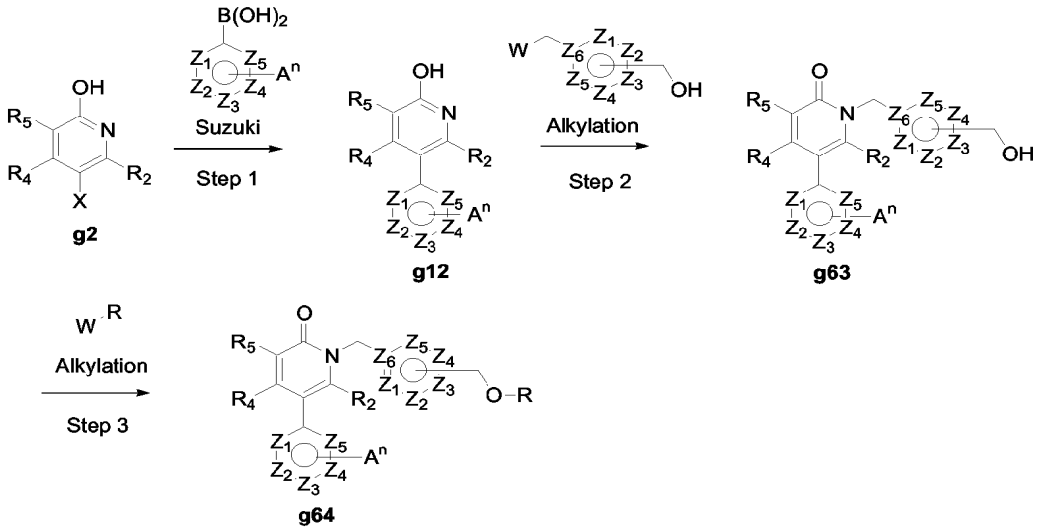
Scheme 22

Another embodiment of the invention provides compounds of Formula (V-b) (Scheme 23). Step 1, nucleophilic displacement of 2-halopyridine **g58** (where X = I, Br, Cl or F) by sodium methoxide in methanol yielded 2-methoxypyridine **g59**. Bromination was achieved using bromine, aqueous potassium bromide, potassium hydroxide and water (Step 2). The bromopyridine **g60** was then functionalized by carbon-carbon bond forming reaction (Step 3, exemplified here by Suzuki-Miyaura reaction) under conditions similar to those described in Scheme 3. Step 4, alkylation was then performed as described in Scheme 2 to give compound **g62**.



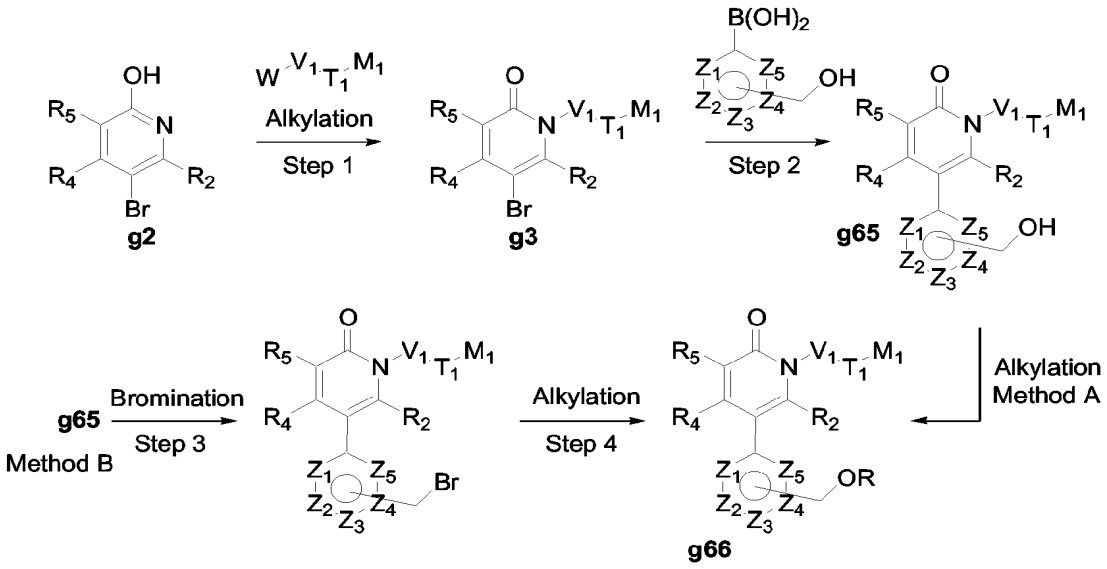
Scheme 23

Another embodiment of the invention provides compounds of Formula (V-b) (Scheme 24). Step 1, substituted pyridine **g2** (where X = Br, I or TfO) was first functionalized by carbon-carbon bond forming reaction (Step 1, exemplified here by Suzuki-Miyaura reaction) under conditions similar to those described in Scheme 3. Alkylation was performed with alkyl halides (W-R_1), NaI in MeCN at 70°C (Step 2). The resulting alcohol **g63** was alkylated using standard Williamson ether synthesis (Step 3, NaH, DMF and alkyl halide at 0°C) to yield compound **g64**.



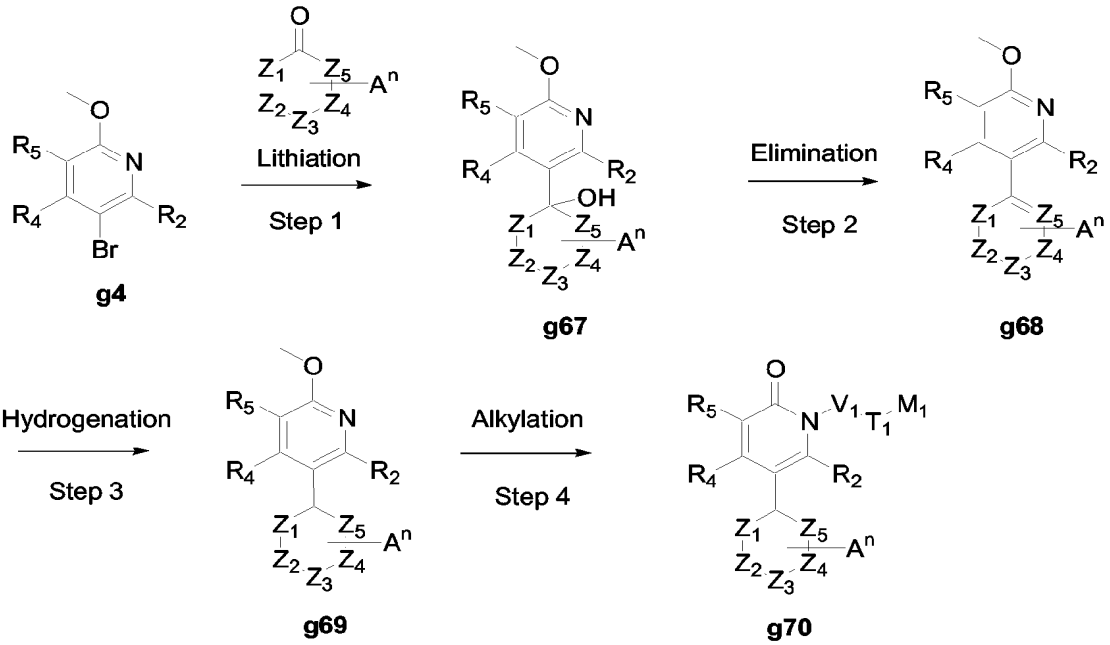
Scheme 24

Another embodiment of the invention provides compounds of Formula (V-b) (Scheme 25). Alkylation of 2-hydroxypyridine **g2** was performed as described in example 1. Step 2, bromopyridine 3 was first functionalized by carbon-carbon bond forming reaction (exemplified here by Suzuki-Miyaura reaction) under conditions similar to those described in Scheme 3. The alcohol **g65** was then alkylated to obtain compound **g66**. Or bromination of compound **g65** was achieved using PPh_3, NBS and Et_20 at -20°C (Step 3). The resulting bromide was alkylated using standard Williamson ether synthesis to yield ether **g66** (Step 4, alkyl alcohol, NaH and DMF at 0°C).



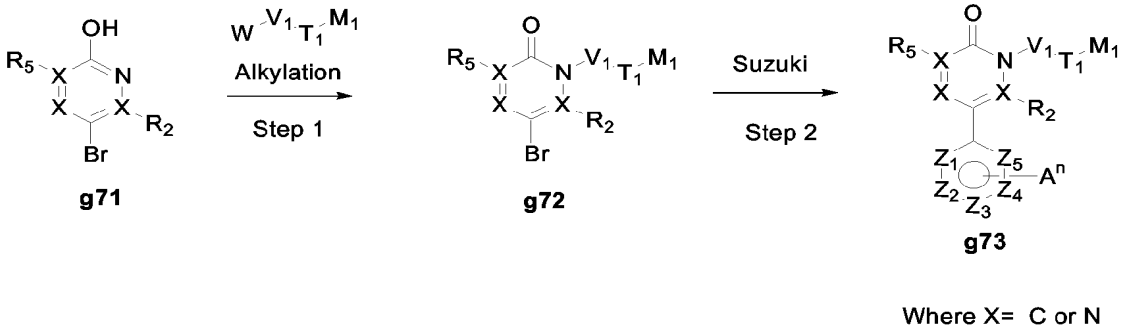
Scheme 25

Another embodiment of the invention provides compounds of Formula (V-b) (Scheme 26). Step 1, lithium-halogen exchange on substituted 5-bromo-2-methoxy-pyridine **g4** at -78°C in THF with butyl lithium was reacted with a substituted carbonyl compounds. The resulting alcohol **g67** was then eliminated using MsCl, TEA and DCM at room temperature (Step 2). The olefin **g68** was then hydrogenated using standard conditions (H_2, Pd/C in EtOH). Finally, the compound was alkylated as described for Scheme 2 to give compound **g70**.



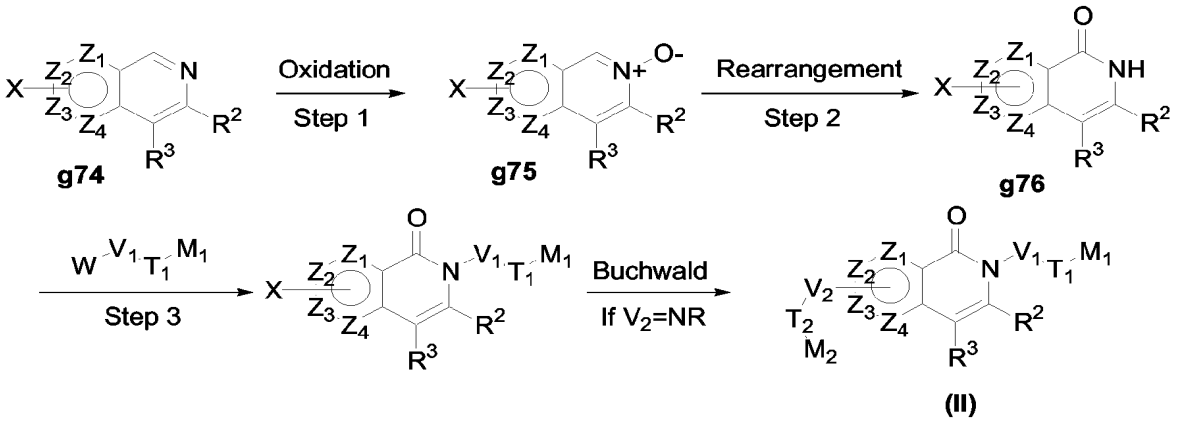
Scheme 26

Another embodiment of the invention provides compounds of Formula (I) (Scheme 27). Where W is Cl, Br, I and OTf, pyrazine **g71** was alkylated using standard conditions (Step 1). NaH, DMF or K_2CO_3, MeCN, at room temperature, elevated temperatures or with microwave irradiation. Alternatively, where W is OH, alkylation could be performed by Mitsunobu reaction using, DEAD, PPh_3, THF at room temperature or 60°C. The bromopyrazine **g72** was then subjected to a carbon-carbon bond forming reaction (Step 2, exemplified here by Suzuki-Miyaura reaction) under conditions similar to those described in Scheme 3 to give compound **g73**.



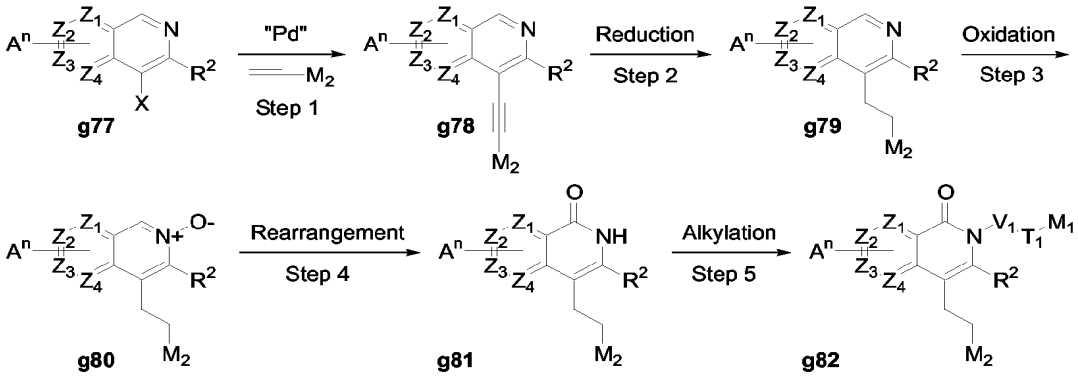
Scheme 27

In another embodiment of the present invention, the compounds of Formula (II) may be prepared according to the synthetic sequences illustrated in Scheme 28. Isoquinoline **g74** can be converted into isoquinolone **g76** (Heterocycles, 1996, 42, 415) *via* oxidation with mCPBA followed by rearrangement of the *N*-oxide in the presence of acetic anhydride and then by basic sodium hydroxide cleavage. Finally, the resulting isoquinolone **g76** can be alkylated as described in Scheme 1 and submitted to Buchwald coupling (if V_2=NR) as in Scheme 22. It is obvious that introduction of $V_1T_1M_1$ or $V_2T_2M_2$ groups can be done through the same process as described earlier.



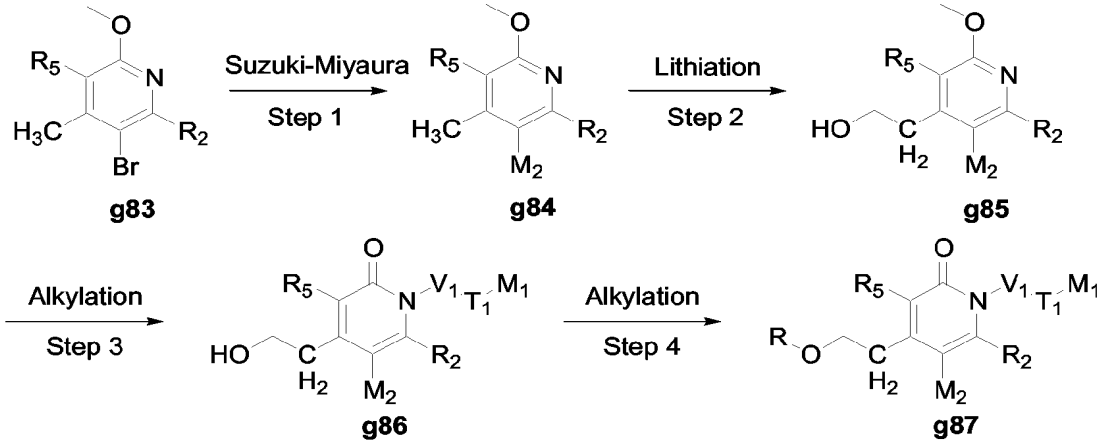
Scheme 28

In another embodiment of the present invention, the compounds of Formula (II) may be prepared according to the synthetic sequences illustrated in Scheme 29. Compound **g77** can be submitted to a Sonogashira coupling and reduced (Scheme 8) to yield compound **g79**. Then the isoquinoline may be transformed into alkylated isoquinolone **g82** as presented in Scheme 29.



Scheme 29

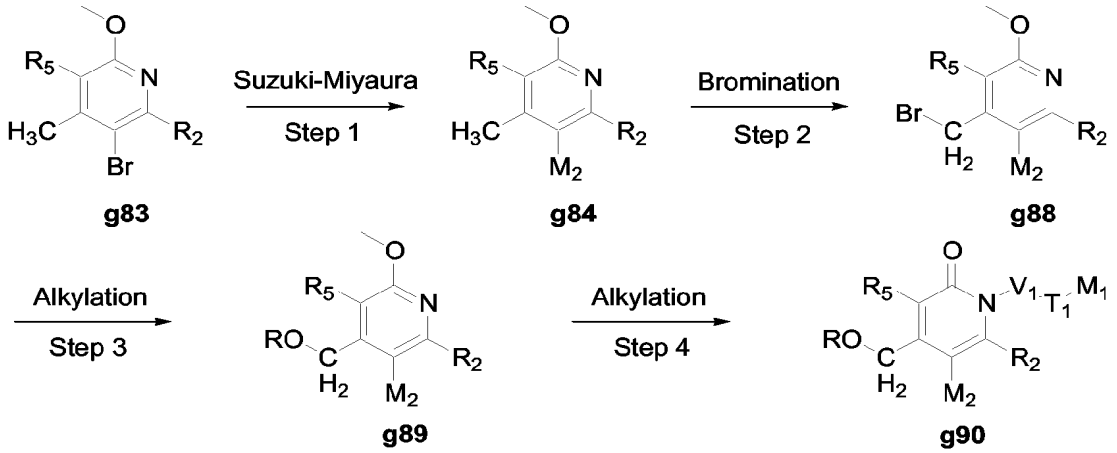
In another embodiment of the present invention, compounds of Formula (V-b) can be prepared in accordance with Scheme 30. Bromopyridine **g83** can be functionalized by carbon-carbon bond forming reaction (exemplified here by Suzuki-Miyaura reaction) under condition similar to those described in Scheme 3. The resulting pyridine **g84** can be lithiated by strong base such as butyl lithium or LDA in THF at low temperatures (*e.g.* -78°C) and subsequently quenched with paraformaldehyde to give alcohol **g86** after workup. N-Alkylation by NaI in acetonitrile at elevated temperatures using W-$V_1T_1M_1$ yields compound **g86**. The resulting alcohol **g86** can be alkylated by the methods described in Scheme 24, step 3.



Scheme 30

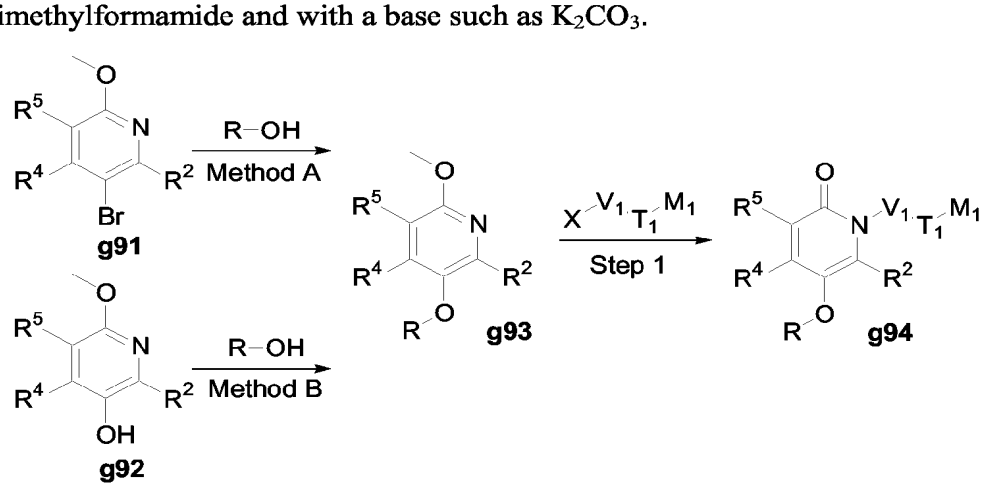
In another embodiment of the present invention, compounds of Formula (V-b) can be prepared in accordance with Scheme 31. Pyridine **g84** was prepared as described in Scheme 30. Bromination with NBS under UV light in CCl_4 at reflux gave compound

g88. Alkylation using ROH and sodium methoxide at reflux gave compound **g89**. The resulting alcohol **g89** can then be alkylated by the methods described in Scheme 1.



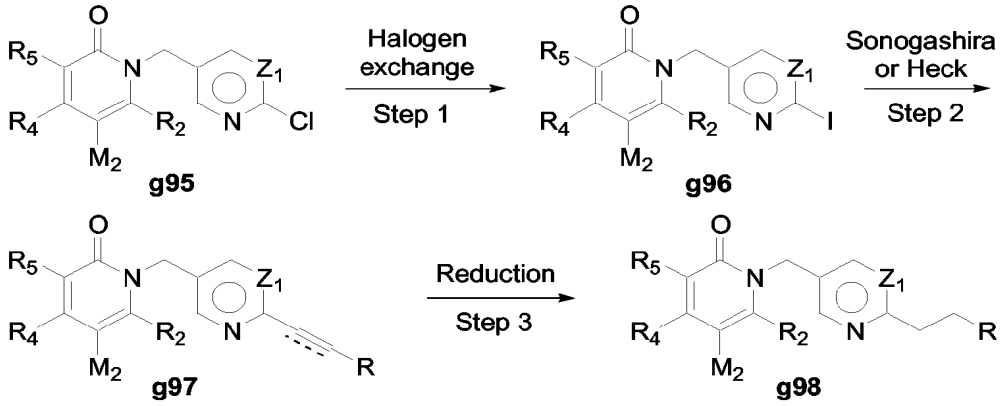
Scheme 31

Compound **g93** (Scheme 32) can be synthesized from either bromide **g91** or alcohol **g92** using any one of the procedures known in the art, for example, using a copper catalyzed coupling reaction conditions when R is aryl or *via* a Mitsunobu reaction conditions when R is alkyl respectively. Finally, the resulting ether **g93** can be alkylated with for example alkyl halide, in an organic solvent such as acetonitrile or dimethylformamide and with a base such as K_2CO_3.



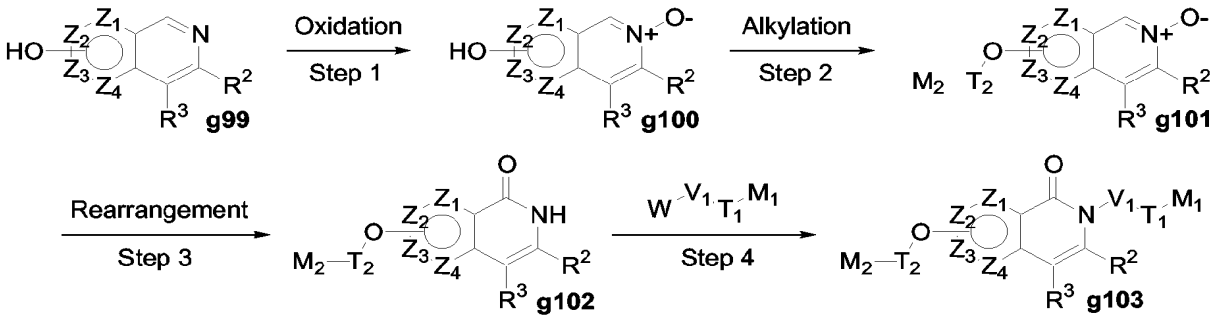
Scheme 32

Compound **g96** (Scheme 33) can be synthesized from pyridine **g95** (prepared as described in Schemes 1 and 3) *via* halogen exchange. Then the iodopyridine may be coupled through Sonogashira or Heck conditions to alkynes or alkenes respectively. The resulting insaturated compound **g97** can then be reduced as exemplified earlier by hydrogenation to give compound **g98**.



Scheme 33

In another embodiment of the present invention, the compounds of Formula (II) may be prepared according to the synthetic sequences illustrated in Scheme 34. Isoquinoline **g99** can be converted into his *N*-oxide **g100** *via* oxidation in the presence of MCPBA followed by standard alkylation. Rearrangement of *N*-oxide **g101** in the presence of acetic anhydride and basic sodium hydroxide cleavage yielded isoquinolone **g102**. Finally, the resulting isoquinolone **g102** can be alkylated as described in Scheme 1. It is obvious that introduction of $V_1T_1M_1$ or $V_2T_2M_2$ groups can be done through the same process as described earlier.



Scheme 34

EXPERIMENTAL

Several methods for preparing the compounds of this invention are illustrated in the following Examples.

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification.

Specifically, the following abbreviations may be used in the examples and throughout the specification.

AcOEt (ethyl acetate)	M (molar)
AcOH (acetic acid)	MeOH (methanol)
BBr_3 (boron tribromide)	mg (milligrams)
BINAP (±-1,1'-Bi(2-naphthol)	$MgSO_4$ (magnesium sulphate)
Br_2 (bromine)	MHz (megahertz)
$CDCl_3$ (deuterated chloroform)	min (minutes)
CCl_4 (carbon tetrachloride)	µL(microliters)
CH_2Cl_2 (dichloromethane)	mL (milliliters)
MCPBA (3-chloroperbenzoic acid)	mmol (millimoles)
DEAD (diethyl azodicarboxylate)	M.p. (melting point)
DIBAL (diisobutyl aluminium hydride)	$NaBH(OAc)_3$ (sodium borohydride triacetate)
DME (dimethoxyethane)	Na_2CO_3 (sodium carbonate)
DMF (dimethylformamide)	NaH (sodium hydride)
DMSO (dimethyl sulfoxide)	$NaHCO_3$ (sodium hydrogenocarbonate)

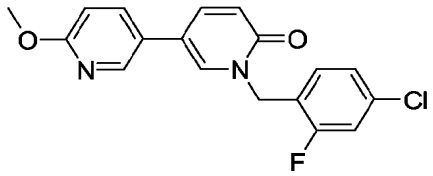
Dppf (1,1'-bis(diphenylphosphanyl)ferrocene)	NaHMDS (sodium hexamethyldisilazane)
EDCI.HCl (1-3(dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride)	NaI (sodium iodide)
Et_3N (triethylamine)	NaO^tBu (sodium *tert*-butoxide)
Et_2O (diethyl ether)	Na_2SO_4 (sodium sulphate)
EtOH (ethanol)	NBS (N-bromosuccinimide)
g (grams)	NH_4Cl (ammonium chloride)
^1H (proton)	NH_4OH (ammonium hydroxide)
H_2 (hydrogen)	NMR (Nuclear Magnetic Reasonance)
HCl (hydrochloric acid)	$Pd_2(dba)_3$ (palladium (II)dibenzylideneacetone)
HPLC (High Pressure Liquid Chromatography)	$PdCl_2(dppf)_2$ (Bis(1,1'-bis(diphenylphosphanyl)ferrocene palladium (II) dichloride)
Hz (Hertz)	$PdCl_2(PPh_3)_2$ (Bis(triphenylphosphine) palladium (II) dichloride
KBr (potassium bromide)	$Pd(OAc)_2$
K_2CO_3 (potassium carbonate)	$Pd(PPh_3)_4$ (tetrakis(triphenylphosphine)palladium(0))
KOAc (potassium acetate)	PPh_3 (triphenylphosphine)
KI (potassium iodide)	Rf
KO*t*Bu (potassium *tert*-butoxide)	RT (Retention Time)
KOH (potassium hydroxide)	TFA (trifluoroacetic acid)
K_3PO_4 (potassium phosphate)	THF (tetrahydrofuran)
LCMS (Liquid Chromatography Mass Spectrum)	TLC (thin layer chromatography)
$LiAlH_4$ (lithium aluminium hydride)	

All references to brine refer to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Celsius). All reactions are conducted not under an inert atmosphere at room temperature unless otherwise noted.

The microwave oven used is an apparatus from Biotage (Optimizer™) equipped with an internal probe that monitors reaction temperature and pressure, and maintains the desired temperature by computer control.

EXAMPLES

EXAMPLE 1 : 1-(4-Chloro-2-fluorobenzyl)-5-(6-methoxypyridin-3-yl)pyridin-2(1*H*)-one (Final Compound 6-51)



Step 1 : 5-Bromopyridin-2(1H)-one

According to Scheme 1 Step 1: A mixture of 2-hydroxypyridine (1eq, 100mmol, 10.0g) in AcOH (100mL) was treated with NBS (1.06eq, 110mmol, 19.8g) at room temperature for 4 hours. The mixture was concentrated, azeotroped twice with EtOH then the solid was taken up in hot EtOH (100mL). After cooling to room temperature, the precipitate was removed by filtration and recrystallized from EtOH to provide 5-bromopyridin-2(1*H*)-one (51.7mmol, 9.00g, 49%) as a pale brown solid.

Rf = 0.60 (AcOEt/MeOH/NEt_3 100/15/1); LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 0.59-2.46min; MS *m/z* (CI) $[MH]^+$= 174, 176.

Step 2 : 1-(4-Chloro-2-fluorobenzyl)-5-bromopyridin-2(1H)-one

According to Scheme 1 Step 2: K_2CO_3 (10eq, 0.11mmol, 16.0g) and 1-(bromomethyl)-4-chloro-2-fluorobenzene (1.5eq, 17.0mmol, 3.90g) was added to a solution of 5-bromopyridin-2(1*H*)-one (1eq, 11.0mmol, 2.00g), in THF (100mL). The suspension was stirred for 2 hours at room temperature and 17 hours at 60°C. The reaction mixture was filtered and the mother liquor was concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 70g SiO_2) using CH_2Cl_2/AcOEt 80/20 as eluent to afford the title compound 1-(4-chloro-2-fluorobenzyl)-5-bromopyridin-2(1*H*)-one (9.10mmol, 2.87g, 79%) as a white solid.

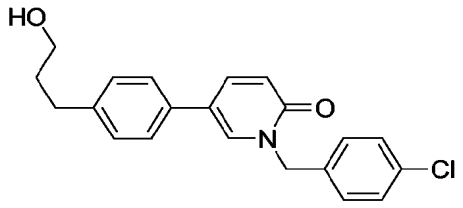
LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 4.12min; MS *m/z* (CI) $[MH]^+$= 316, 318.

Step 3 : 1-(4-Chloro-2-fluorobenzyl)-5-(6-methoxypyridin-3-yl)pyridin-2(1H)-one

According to Scheme 3 Method A: To a mixture of 1-(4-chloro-2-fluorobenzyl)-5-bromopyridin-2(1*H*)-one (1eq, 1.00mmol, 0.40g) in dioxane/K_3PO_4 (2M, 10mL), were added $Pd(PPh_3)_4$ (0.3eq, 0.4mmol, 0.4g) and 6-methoxypyridin-3-ylboronic acid (1.5eq, 2.00mmol, 0.30g) then the reaction mixture was heated at 80°C for 17 hours. The mixture was diluted with AcOEt. The organic fraction was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 25g SiO_2, CH_2Cl_2/AcOEt 70/30) and by crystallization in pentane/Et_2O to afford 1-(4-chloro-2-fluorobenzyl)-5-(6-methoxypyridin-3-yl)pyridin-2(1*H*)-one (0.91mmol, 0.40g, 91%) as a white solid.

M.p.: 136°C; LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 4.13min; MS *m/z* (CI) $[MH]^+$= 345, 347; ^1H NMR (300MHz, DMSO-d^6) δ 3.87 (s, 3H), 5.17 (s, 2H), 6.53 (d, J=9.5Hz, 1H), 6.89 (d, J=8.7Hz, 1H), 7.17-7.24 (m, 1H), 7.27 (dd, J=2.0Hz and 8.4Hz, 1H), 7.46 (dd, J=2.0Hz and 10.2Hz, 1H), 7.84-7.94 (m, 2H), 8.20 (d, J=2.6Hz, 1H), 8.38 (d, J=2.3Hz, 1H).

EXAMPLE 2 : 1-(4-Chlorobenzyl)-5-(4-(3-hydroxypropyl) phenyl) pyridin-2(1*H*)-one (Final Compound 2-16)



Step 1 : 1-(4-Chlorobenzyl)-5-bromopyridin-2(1H)-one

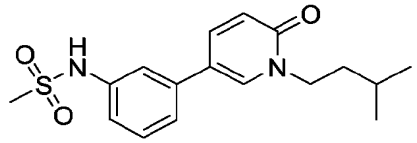
According to Scheme 1 Step 2: The title compound was prepared from 5-bromopyridin-2(1*H*)-one (1eq, 29.0mmol, 5.00g, Example 1 Step 1) and 4-chlorobenzyl bromide (1.2eq, 34.0mmol, 7.10g) according to the procedure described for Example 1 Step 2. After concentration of the solvent, water was added. The aqueous phase was extracted with AcOEt and the combined organic fractions were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was recristallized with pentane/Et_2O 50/50 to afford 1-(4-chlorobenzyl)-5-bromopyridin-2(1*H*)-one (26.2mmol, 7.82g, 91%) as a white solid.

LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 4.18min; MS *m/z* (CI) $[MH]^+$= 299, 301.

Step 2 : 1-(4-Chlorobenzyl)-5-(4-(3-hydroxypropyl)phenyl)pyridin-2(1H)-one

According to Scheme 3 Method Λ: To a solution of 1-(4-chlorobenzyl)-5-bromopyridin-2(1*H*)-one (1eq, 0.33mmol, 0.10g) in dioxane/saturated aqueous $NaHCO_3$ (1:1, 6mL) was added $Pd(PPh_3)_4$ (0.15eq, 0.05mmol, 58mg) and 4-(3-hydroxypropyl)phenylboronic acid (1.5eq, 0.50mmol, 90.0mg). The reaction was then stirred at 90°C for 4.5 hours. The reaction was allowed to cool and diluted with AcOEt. The reaction was washed with saturated NH_4Cl solution, brine and the organic phase extracted (x3). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 15g SiO_2) using pure AcOEt as the eluent to afford 1-(4-chlorobenzyl)-5-(4-(3-hydroxypropyl)phenyl)pyridin-2(1*H*)-one (0.22 mmol, 78 mg, 66%) as a white solid.
M.p.: 165°C; Rf = 0.05 (CH_2Cl_2/AcOEt 80/20); LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 3.78min; MS *m/z* (CI) $[MH]^+$= 354, 356; ^1H NMR (300MHz, DMSO-d^6) δ 1.64-1.77 (m, 2H), 2.61 (t, J=7.3Hz, 2H), 3.32-3.46 (m, 2H), 4.48 (t, J=5.1Hz, 1H), 5.15 (s, 2H), 6.52 (d, J=9.5Hz, 1H), 7.24 (d, J=8.1Hz, 2H), 7.35-7.44 (4H), 7.47 (d, J=8.1Hz, 2H), 7.83 (dd, J=2.6Hz, 9.5Hz, 1H), 8.23 (d, J=2.6Hz, 1H).

EXAMPLE 3 : *N*-(3-(1-Isopentyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)methanesulfonamide (Final Compound 8-02)



Step 1 : 5-Bromo-1-isopentylpyridin-2(1H)-one

According to Scheme 1 Step 2: The title compound was prepared from 5-bromopyridin-2(1*H*)-one (1eq, 0.01mol, 1.73g) and 1-isopentylbromide (1eq, 0.01mmol, 1.51g) according to the procedure described for Example 1 Step 2. Reaction conditions: 3 hours under reflux in acetonitrile. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column SiO_2) using

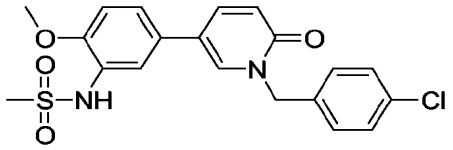
CH_2Cl_2/AcOEt (80/20) as the eluent to afford 5-bromo-1-isopentylpyridin-2(1*H*)-one (6.23mmol, 1.52g, 62%) as a brown oil.

Step 2 : N-(3-(1-Isopentyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)methanesulfonamide

According to scheme 3 Method Λ: The title compound was prepared from 5-bromo-1-isopentylpyridin-2(1*H*)-one (1eq, 0.41mmol, 0.10g) and 3-(methylsulfonamido)phenylboronic acid (1.5eq, 0.61mmol, 0.13g) according to the procedure described for Example 2 Step 2. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 15g SiO_2) using CH_2Cl_2/AcOEt (80/20) as the eluent to afford N-(3-(1-isopentyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)methanesulfonamide (0.32mmol, 0.11g, 77%) as a white solid.

M.p.:159°C; Rf = 0.42 (CH_2Cl_2/AcOEt 50/50); LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 3.49min; MS *m/z* (CI) $[MH]^+$= 335; ^1H NMR (300MHz, DMSO-d^6) δ 0.93 (d, 6H), 1.49-1.62 (m, 3H), 3.02 (s, 3H), 3.91-4.00 (m, 2H), 6.48 (d, J=9.4Hz, 1H), 7.10-7.18 (m, 1H), 7.28-7.42 (m, 3H), 7.70 (dd, J=2.6Hz, 9.4Hz, 1H), 8.03 (d, J=2.6Hz, 1H), 9.78 (s, 1H).

EXAMPLE 4 : *N*-(5-(1-(4-Chlorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-2-methoxyphenyl)methanesulfonamide (Final Compound 2-56)



Step 1 : 4-Methoxy-3-(methylsulfonamido)phenylboronic acid

To a solution of 3-amino-4-methoxyphenylboronic acid (1eq, 2.10mmol, 0.35g) in CH_2Cl_2 (5mL) at -78°C was added Et_3N (6eq, 13.0mmol, 1.7mL). The reaction was stirred for 30 minutes then methanesulfonyl chloride (1.1eq, 2.30mmol, 0.26g) was added. The reaction was then stirred at -78°C for 1 hour. The reaction was allowed to warm to room temperature and diluted with CH_2Cl_2. The reaction was washed with 1.0N aqueous HCl and the organic phase was extracted (x3). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated under reduced pressure to

afford 4-methoxy-3-(methylsulfonamido)phenylboronic acid (1.92mmol, 0.49g, 96%) as a white solid.

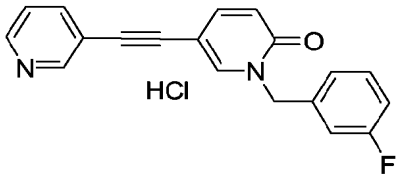
LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 2.11min; MS *m/z* (CI) $[MH]^+$= 246.

Step 2 : N-(5-(1-(4-Chlorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-2-methoxyphenyl) methane sulphonamide

According to Scheme 3 Method A: The title compound was prepared from 1-(4-chlorobenzyl)-5-bromopyridin-2(1*H*)-one (1eq, 1.80mmol, 0.55g, Example 2 Step 1) and 4-methoxy-3-(methylsulfonamido)phenylboronic acid (1.1eq, 2.00mmol, 0.49g) according to the procedure described for Example 1 Step 3. Reaction conditions: 4 hours at 80°C. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g SiO_2) using CH_2Cl_2/AcOEt (90/10) then recrystallized from pentane/Et_2O to afford N-(5-(1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-2-methoxyphenyl)methanesulphonamide (0.31mmol, 0.32g, 41%) as a white solid.

M.p.: 151°C; LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 3.75min; MS *m/z* (CI) $[MH]^+$= 419, 421; ^1H NMR (300MHz, DMSO-d^6) δ 2.88 (s, 3H), 3.76 (s, 3H), 5.08 (s, 2H), 6.44 (d, J=10.9Hz, 1H), 7.05 (d, J=10.9Hz, 1H), 7.27-7.35 (m, 3H), 7.42-7.60 (m, 3H), 7.68 (dd, J=3.5Hz, J=10.9Hz, 1H), 8.08 (d, J=3.5Hz, 1H), 8.94 (s, 1H).

EXAMPLE 5 : 1-(3-Fluorobenzyl)-5-(2-(pyridin-3-yl)ethynyl)pyridin-2(1*H*)-one hydrochloride (Final Compound 7-02)



Step 1 : 1-(3-Fluorobenzyl)-5-bromopyridin-2(1H)-one

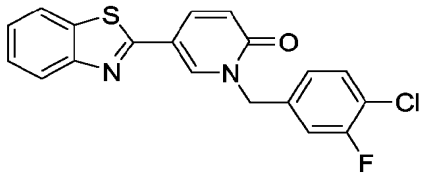
According to Scheme 1 Step 2: 1-(3-Fluorobenzyl)-5-bromopyridin-2(1*H*)-one was prepared from 5-bromopyridin-2(1*H*)-one (Example 1 Step 1) and 3-fluorobenzyl bromide according to the procedure described for Example 2 Step 1. The crude product

was washed with pentane/Et_2O 50/50 to afford 1-(3-fluorobenzyl)-5-bromopyridin-2(1*H*)-one (10.7mmol, 3.00g, 62%) as a white solid.
LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 4.05min; MS *m/z* (CI) $[MH]^+$= 283.

Step 2 : 1-(3-Fluorobenzyl)-5-(2-(pyridin-3-yl)ethynyl)pyridin-2(1H)-one hydrochloride

According to Scheme 3 Method B: Copper iodide (0.1eq, 6.7mg, 35µmol) and Et_3N (20eq, 7.09mmol, 1.00mL) in DMF (5mL) were stirred under nitrogen for 10 min. $PdCl_2(PPh_3)_2$ (0.1eq, 35µmol, 25mg) was added to the reaction mixture and the reaction mixture was stirred for a further 15 min at room temperature. 1-(3-Fluorobenzyl)-5-bromopyridin-2(1*H*)-one (1eq, 0.35mmol, 0.10g) and 3-ethynylpyridine (1.2eq, 0.43mmol, 0.04g) were successively added to the reaction mixture. After stirring at 80°C for 4 hours, the reaction mixture was quenched with water and the aqueous layer was washed with AcOEt (3x30mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel using CH_2Cl_2/AcOEt 90/10 + 1% HCl 2M in dioxane as eluent. 1-(3-Fluorobenzyl)-5-(2-(pyridin-3-yl)ethynyl)pyridin-2(1*H*)-one hydrochloride was obtained as a beige solid (32 µmol, 11mg, 9%).
M.p.: 179°C; LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 3.68 min; MS *m/z* (CI) $[MH]^+$= 305; ^1H NMR (500MHz, DMSO-d^6) δ 5.12 (s, 2H), 6.50 (d, J=9.4Hz, 1H), 7.11-7.20 (3H), 7.37-7.43 (m, 1H), 7.51 (dd, J=5.0Hz and 8.0Hz, 1H), 7.58 (dd, J=2.5Hz and 9.4Hz, 1H), 7.96-8.00 (m, 1H), 8.37 (d, J=2.4Hz, 1H), 8.59 (dd, J=1.6Hz and 5.0Hz, 1H), 8.73 (d, J=2.1Hz, 1H).

EXAMPLE 6 : 1-(4-Chloro-3-fluorobenzyl)-5-(benzo[*d*]thiazol-2-yl)pyridin-2(1*H*)-one (Final Compound 6-19)



Step 1 : 2-(6-Methoxypyridin-3-yl)benzo[d]thiazole

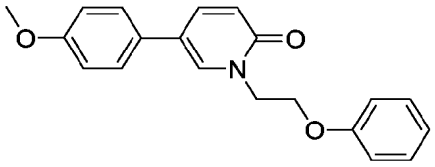
According to Scheme 4 Method A: The title compound was prepared from 2-bromobenzo[*d*]thiazole (1eq, 0.91mmol, 0.20g) and 6-methoxypyridin-3-ylboronic acid (1.5eq, 1.36mmol, 0.21g) according to the procedure described for Example 2 Step 2. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 25g SiO_2) using cyclohexane/AcOEt 95/5 as eluent to afford 2-(6-methoxypyridin-3-yl)benzo[*d*]thiazole (0.74mmol, 0.18g, 82%) as a white solid.

Step 2 : 1-(4-Chloro-3-fluorobenzyl)-5-(benzo[d]thiazol-2-yl)pyridin-2(1H)-one

According to Scheme 4, Step 1: A mixture of 2-(6-methoxypyridin-3-yl)benzo[*d*]thiazole (1eq, 0.25mmol, 60mg), NaI (5eq, 1.20mmol, 0.19g) and 4-chloro-3-fluorobenzylbromide (5eq, 1.20mmol, 0.28g) in acetonitrile (10mL) was stirred for 14 hours at 90°C. The crude residue was partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 25g SiO_2) using CH_2Cl_2/AcOEt 95/5 as eluent to afford 1-(4-chloro-3-fluorobenzyl)-5-(benzo[*d*]thiazol-2-yl)pyridin-2(1*H*)-one (0.14mmol, 0.05g, 58%) as a beige solid.

M.p.:164°C; LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 4.89min; MS *m/z* (CI) $[MH]^+$= 371, 373; ^1H NMR (500MHz, $CDCl_3$) δ 5.26 (s, 2H), 6.61 (d, J=9.5Hz, 1H), 7.22-7.25 (m, 1H), 7.41-7.45 (m, 1H), 7.45-7.48 (m, 1H), 7.50-7.54 (m, 1H), 7.56-7.60 (m, 1H), 7.96 (d, J=7.7Hz, 1H), 8.11 (dd, J=2.7Hz and 9.5Hz, 1H), 8.11-8.13 (m, 1H), 8.81 (d, J=2.6Hz, 1H).

EXAMPLE 7 : 5-(4-Methoxyphenyl)-1-(2-phenoxyethyl)pyridin-2(1*H*)-one (Final Compound 5-18)



Step 1 : 5-(4-Methoxyphenyl)-(1H)-pyridin-2-one

According to Scheme 5 Step 1: The title compound was prepared from 5-bromopyridin-2(1*H*)-one (1eq, 17.2mmol, 3.00g, Example 1 Step 1) and 4-methoxyphenylboronic acid (1.5eq, 25.9mmol, 3.93g) according to the procedure described for Example 2 Step 2. Reaction conditions: 4.5 hours at 120°C. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 70g SiO_2) using pure AcOEt then AcOEt/MeOH 95/5 as eluent to afford 5-(4-methoxyphenyl)-(1*H*)-pyridin-2-one (11.9mmol, 2.40g, 69%) as a white solid.

Rf = 0.48 (AcOEt/MeOH 90/10); LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 2.56min; MS *m/z* (CI) $[MH]^+$ = 202.

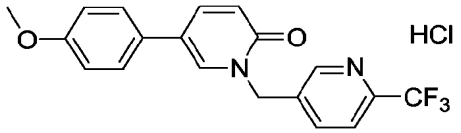
Step 2 : 5-(4-Methoxyphenyl)-1-(2-phenoxyethyl)pyridin-2(1H)-one

According to Scheme 5 Step 2: To a solution of 5-(4-methoxyphenyl)-(1*H*)-pyridin-2-one (1eq, 0.30mmol, 60mg) in THF (3mL) was added K_2CO_3 (10eq, 3.00mmol, 0.41g). The reaction was stirred at room temperature for 30 minutes then 1-(2-bromoethoxy)benzene (3eq, 0.90mmol, 0.18g) was added. The reaction was stirred at 60°C for 12 hours. After concentration of the solvent, acetonitrile (3mL) was added followed by K_2CO_3 (10eq, 3.00mmol, 0.41g) and 1-(2-bromoethoxy)benzene (10eq, 3.00mmol, 0.60g) then the reaction was microwaved for 5 minutes at 180°C. The reaction was filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 10g SiO_2) using CH_2Cl_2/AcOEt (80/20) as the eluent to afford 5-(4-methoxyphenyl)-1-(2-phenoxyethyl)pyridin-2(1*H*)-one (0.13mmol, 42mg, 44%) as a yellow oil.

Rf = 0.29 (CH_2Cl_2/AcOEt 90/10); LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 4.31min; MS *m/z* (CI) $[MH]^+$ = 322; ^1H NMR (500MHz, $CDCl_3$) δ 3.86 (s, 3H), 4.33-

4.37 (m, 2H), 4.38-4.43 (m, 2H), 6.67 (d, J=10.1Hz, 1H), 6.87-6.90 (m, 2H), 6.95-6.99 (m, 3H), 7.25-7.30 (m, 2H), 7.32-7.35 (m, 2H), 7.59-7.62 (m, 2H).

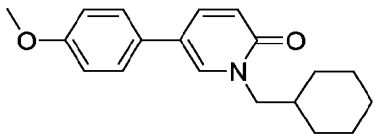
EXAMPLE 8 : 5-(4-Methoxyphenyl)-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)-pyridin-2(1*H*)-one hydrochloride (Final Compound 4-47)



According to Scheme 5 Step 2: The title compound was prepared from 5-(4-methoxyphenyl)-(1*H*)-pyridin-2-one (1eq, 0.50mmol, 0.10g, Example 7 Step 1) and 5-(chloromethyl)-2-(trifluoromethyl)pyridine (1.5eq, 0.74mmol, 0.15g) according to the procedure described for Example 1 Step 2. Reaction conditions: 6 hours at 70°C and 48 hours at room temperature. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 10g SiO_2, CH_2Cl_2/AcOEt 90/10). The purified oil was dissolved in Et_2O and HCl (4M in dioxane) was added. The resulting precipitate was filtered, dried to afford 5-(4-methoxyphenyl)-1-((6-(trifluoromethyl)pyridin-3-yl)methyl)pyridin-2(1*H*)-one hydrochloride (83µmol, 30mg, 17%) as a white solid.

M.p.: 168°C; LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 4.06min; MS *m/z* (CI) $[MH]^+$= 361; ^1H NMR (500MHz, $CDCl_3$) δ 3.76 (s, 3H), 5.27 (s, 2H), 6.51 (d, J=9.4Hz, 1H), 6.98 (d, J=6.7Hz, 2H), 7.51 (d, J=6.7Hz, 2H), 7.83 (dd, J=2.7Hz and 9.4Hz, 1H), 7.88 (d, J=8.2Hz, 1H), 8.00 (dd, J=1.7Hz and 8.2Hz, 1H), 8.28 (d, J=2.5Hz, 1H), 8.81 (d, J=1.7Hz, 1H).

EXAMPLE 9 : 1-(Cyclohexylmethyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (Final Compound 4-03)

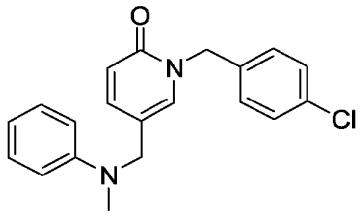


According to Scheme 5 Step 2: To a solution of 5-(4-methoxyphenyl)pyridin-2(1*H*)-one (1eq, 0.35mmol, 70mg, Example 7 Step 1) in acetonitrile (2mL) were added K_2CO_3 (10eq, 3.50mmol, 0.48g) and (bromomethyl)cyclohexane (10eq, 3.50mmol, 0.49mL).

The reaction was microwaved for 10 minutes at 180°C. The reaction was allowed to cool. The reaction was then filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 15g SiO_2) using CH_2Cl_2/AcOEt (80/20, Rf=0.3). The product was further purified by reverse phase C_{18} column using water/acetonitrile 60/40 to afford 1-(cyclohexylmethyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (0.11mmol, 32mg, 31%) as a colorless oil.

LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 4.72min; MS m/z (CI) $[MH]^+$= 298; ^1H NMR (300MHz, $CDCl_3$) δ 0.85-1.09 (m, 2H), 1.09-1.32 (m, 3H), 1.53-1.78 (m, 5H), 1.78-2.00 (m, 1H), 3.74 (d, J=7.3Hz, 2H), 3.77 (s, 3H), 6.57 (d, J=9.4Hz, 1H), 6.88 (d, J=8.7Hz, 2H), 7.29-7.35 (3H), 7.49 (dd, J=2.7Hz, 9.4Hz, 1H).

EXAMPLE 10 : 1-(4-Chlorobenzyl)-5-((methyl(phenyl)amino)methyl)pyridin--2(1*H*)-one (Final Compound 3-07)



Step 1 : 1-(4-Chlorobenzyl)-6-oxo-1,6-dihydropyridine-3-carbaldehyde

According to Scheme 2: The title compound was prepared from 6-methoxynicotinaldehyde (1eq, 13.4mmol, 1.83g) and 4-chloro-benzylbromide (2eq, 26.8mmol, 5.50g) according to the procedure described for Example 6 Step 2. Reaction conditions: 17 hours under reflux. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 25g SiO_2) using CH_2Cl_2/AcOEt 95/5 as eluent to afford 1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridine-3-carbaldehyde (9.08mmol, 2.25g, 68%) as an orange solid.

LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 3.51min; MS *m/z* (CI) $[MH]^+$= 248.

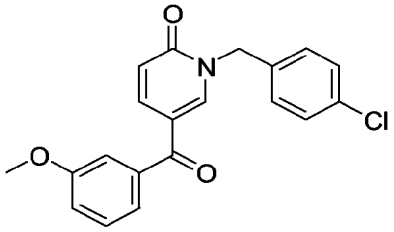
Step 2 : 1-(4-Chlorobenzyl)-5-((methyl(phenyl)amino)methyl)pyridin-2(1H)-one

According to Scheme 7 Method A: A solution of *N*-methylbenzenamine (1eq, 0.40mmol, 0.04mL) and 1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridine-3-carbaldehyde

(1eq, 0.40mmol, 0.10g) in CH_2Cl_2 (8mL) was stirred for 10 min. at room temperature then AcOH (1eq, 0.40mmol, 0.02mL) and $NaBH(OAc)_3$ (1.5eq, 0.60mmol, 0.10g) were added. The reaction mixture was stirred 3 hours at room temperature, was quenched with water and the aqueous phase was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered and evaporated. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 25g SiO_2) using CH_2Cl_2/MeOH 95/5 followed by crystallization in pentane/diisopropyl ether to afford 1-(4-chlorobenzyl)-5-((methyl(phenyl)amino)methyl)pyridin-2(1*H*)-one (0.12mmol, 0.04g, 29%) as a white solid.

M.p.: 106°C; LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 4.43min; MS *m/z* (CI) $[MH]^+$= 339, 341; ^1H NMR (500MHz, DMSO-d^6) δ 2.88 (s, 3H), 4.25 (s, 2H), 5.03 (s, 2H), 6.37 (d, J=9.3Hz, 1H), 6.61-6.66 (m, 1H), 6.75 (dd, J=0.9Hz and 8.8Hz, 2H), 7.11-7.17 (m, 2H), 7.21-7.25 (m, 2H), 7.30 (dd, J=2.6Hz and 9.3Hz, 1H), 7.33-7.38 (m, 2H), 7.67 (d, J=2.0Hz, 1H).

EXAMPLE 11 : 1-(4-Chlorobenzyl)-5-(3-methoxybenzoyl)pyridin-2(1*H*)-one (Final Compound 3-12)

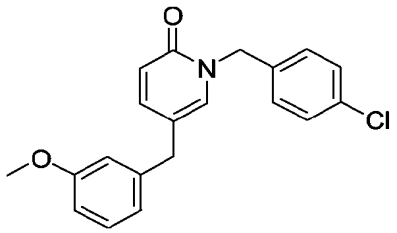


According to Scheme 7 Method C: 1-(4-Chlorobenzyl)-5-(hydroxy(3-methoxyphenyl)-methyl)pyridin-2(1*H*)-one (1eq, 0.28mmol, 0.10g, Example 41) and manganese dioxide (30eq, 8.43mmol, 0.73g) were stirred overnight at room temperature in CH_2Cl_2 (10mL). Upon completion, the crude mixture was filtered through a pad of celite and the filtrate was concentrated. The crude residue was partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum to afford the title compound as a white solid (0.28mmol, 0.10g, 100%).

M.p.: 104°C; LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 4.41 min; MS *m/z* ES^+= 354, 356; ^1H NMR (500MHz, $CDCl_3$) δ 3.83 (s, 3H), 5.13 (s, 2H), 6.65 (d,

J=9.6Hz, 1H), 7.11-7.17 (3H), 7.26-7.29 (m, 2H), 7.33-7.39 (3H), 7.89 (dd, J=2.6Hz and 9.6Hz, 1H), 7.97 (d, J=2.6Hz, 1H).

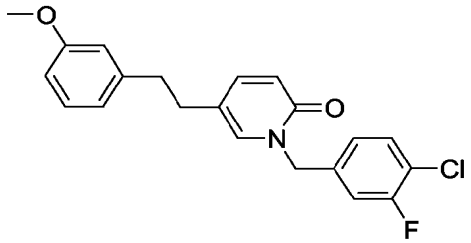
EXAMPLE 12 : 5-(3-Methoxybenzyl)-1-(4-chlorobenzyl)pyridin-2(1*H*)-one (Final Compound 3-02)



According to Scheme 7 Method D**:** Triethylsilane (3eq, 0.84mmol, 0.10g) was added to a solution of 1-(4-chlorobenzyl)-5-(hydroxy(3-methoxyphenyl)methyl)pyridin-2(1*H*)-one (1eq, 0.28mmol, 0.10g, Example 41) in TFA (2mL). The mixture was stirred 1 hour at room temperature. Upon completion, MeOH was added and the solution was evaporated. The crude residue was partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were successively washed with brine, dried over $MgSO_4$ and concentrated under vacuum to afford the crude product. Purification by flash chromatography (AIT Flashsmart prepacked column 10g SiO_2) (CH_2Cl_2/AcOEt 95/5 to 90/10) of the crude product afford the title compound 5-(3-methoxybenzyl)-1-(4-chlorobenzyl)pyridin-2(1*H*)-one (0.20mmol, 0.07g, 71%) as a yellow oil.

LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 4.49 min; MS *m/z* ES^+= 340, 342; ^1H NMR (500MHz, $CDCl_3$) δ 3.65 (s, 2H), 3.78 (s, 3H), 5.08 (s, 2H), 6.57 (d, J=9.3Hz, 1H), 6.63-6.66 (m, 1H), 6.70-6.73 (m, 1H), 6.76-6.80 (m, 1H), 7.02 (d, J=1.9Hz, 1H), 7.18 (dd, J=2.5Hz and 9.3Hz, 1H), 7.21-7.25 (3H), 7.32 (d, J=8.5Hz, 2H).

EXAMPLE 13 : 5-(3-Methoxyphenethyl)-1-(4-chloro-3-fluorobenzyl)pyridin-2(1*H*)-one (Final Compound 7-06)



Step 1 : 5-(3-Methoxyphenethynyl)-2-methoxypyridine

According to Scheme 8 Step 1: Et_3N (15eq, 12.0mmol, 1.68mL), $PdCl_2(PPh_3)_2$ (0.05eq, 0.04mmol, 17.5mg), PPh_3 (0.2eq, 0.16mmol, 41.8mg) and 5-bromo-2-methoxypyridine (1eq, 0.80mmol, 0.15g) were added to a stirred solution of copper iodide (0.05eq, 0.04mmol, 7.6mg) in DMF (8mL). Then 1-ethynyl-3-methoxybenzene (1.1eq, 0.88mmol, 0.12g) was added and the mixture was heated under microwaves (120°C/25min) and was stirred overnight at room temperature. The resulting solution was poured onto water and extracted with AcOEt. The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g SiO_2) using pentane/Et_2O 98/2 as eluent to afford 5-(3-methoxyphenethynyl)-2-methoxypyridine (0.64mmol, 154mg, 81%) as a colorless oil.
LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 5.13 min; MS *m/z* ES^+= 240.

Step 2 : 2-Methoxy-5-(2-(3-methoxyphenyl)ethyl)pyridine

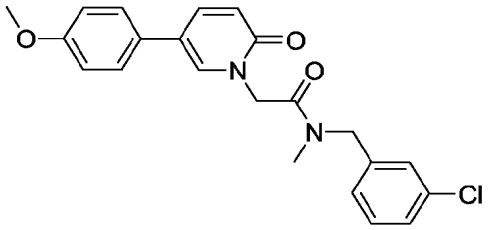
According to Scheme 8 Step 2: A suspension of 5-(3-methoxyphenethynyl)-2-methoxypyridine (1eq, 0.64mmol, 154mg) and Pd/C (15mg) in MeOH (10mL) was stirred overnight at room temperature under H_2 at atmospheric pressure. The resulting mixture was then filtered on a pad of celite and washed with MeOH. The filtrate was concentrated under reduced pressure to afford 2-methoxy-5-(2-(3-methoxyphenyl)ethyl)pyridine (0.49mmol, 0.12g, 77%) as a colorless oil.
LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 4.66 min; MS *m/z* ES^+= 244.

Step 3 : 5-(3-Methoxyphenethyl)-1-(4-chloro-3-fluorobenzyl)pyridin-2(1H)-one

According to Scheme 8 Step 3: The title compound was prepared from 2-methoxy-5-(2-(3-methoxyphenyl)ethyl)pyridine (1eq, 0.25mmol, 0.06g) and 4-chloro-3-fluorobenzylbromide (2eq, 0.49mmol, 0.11g) according to the procedure described for Example 6 Step 2. Reaction conditions: 12 hours at 100°C. The resulting dark brown oil was purified by flash chromatography (AIT Flashsmart prepacked column 25g SiO_2, CH_2Cl_2/MeOH 98/2) to afford 5-(3-methoxyphenethyl)-1-(4-chloro-3-fluorobenzyl)pyridin-2(1*H*)-one (0.14mmol, 55.0mg, 60%) as a yellow oil.

LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 4.68 min; MS *m/z* ES^+= 372, 374; ^1H NMR (500MHz, $CDCl_3$) δ 2.65 (t, J=7.4Hz, 2H), 2.79 (t, J=7.4Hz, 2H), 3.76 (s, 3H), 4.98 (s, 2H), 6.59 (d, J=9.2Hz, 1H), 6.60-6.65 (2H), 6.72-6.75 (m, 1H), 6.79-6.82 (m, 1H), 6.90-6.94 (m, 1H), 6.99 (d, J=2.0Hz and 9.6Hz, 1H), 7.13-7.18 (m, 1H), 7.23 (dd, J=2.5Hz and 9.2Hz, 1H), 7.31-7.36 (m, 1H).

EXAMPLE 14 : *N*-(3-Chlorobenzyl)-2-(5-(4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl)-*N*-methylacetamide (Final Compound 5-24)



Step 1 : Ethyl 2-(5-(4-methoxyphenyl)-2-oxopyridin-1(2H)-yl)acetate

According to Scheme 9 Step 1: The title compound was prepared from 5-(4-methoxyphenyl)pyridin-2(1*H*)-one (1eq, 3.73mmol, 0.75g, Example7 Step 1) and ethylbromoacetate (1.2eq, 4.47mmol, 0.50mL) according to the procedure described for Example 1 Step 2. The reaction was stirred at 60°C for 12 hours.The reaction was filtered and concentrated under reduced pressure to yield a yellow oil. The product was triturated from diisopropyl ether to afford ethyl 2-(5-(4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl)acetate (3.38mmol, 0.97g, 91%) as a white solid.

LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 3.53min; MS *m/z* (CI) $[MH]^+$= 288.

Step 2 : 2-(5-(4-Methoxyphenyl)-2-oxopyridin-1(2H)-yl)acetic acid

According to Scheme 9 Step 2: To a solution of ethyl 2-(5-(4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl)acetate (1eq, 3.38mmol, 0.97g) in water/EtOH (1:1, 20mL) at 0°C was added lithium hydroxide (10eq, 33.8mmol, 1.44g). The reaction was then allowed to warm to room temperature and stirred for 2 hours. The reaction was then cooled to 0°C and acidified with HCl 1M solution till pH=2. The resulting precipitate was filtered under reduced pressure to yield 2-(5-(4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl)acetic acid (2.56mmol, 0.66g, 76%) as a white solid.

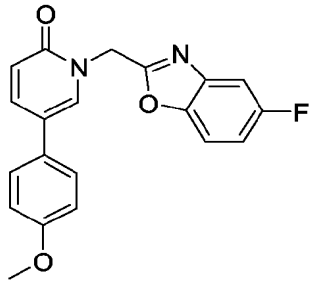
LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 2.89min; MS *m/z* (CI) $[MH]^+$= 260.

Step 3 : N-(3-Chlorobenzyl)-2-(5-(4-methoxyphenyl)-2-oxopyridin-1(2H)-yl)-N-methyl-acetamide

According to Scheme 9 Step 3: To a solution of (3-chlorophenyl)-N-methylmethanamine (1eq, 0.19mmol, 0.03g), 2-(5-(4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl)acetic acid (1eq, 0.19mmol, 0.05g) and hydroxybenzotriazole (1.1eq, 0.21mmol, 0.03g) in CH_2Cl_2 (2mL) at room temperature was added EDCI.HCl (1.5eq, 0.29mmol, 55mg). The reaction was stirred at room temperature for 12 hours then diluted with AcOEt. The reaction was washed with brine and the organic phase extracted (x3). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 10g SiO_2) using CH_2Cl_2/AcOEt (50/50) as eluent to afford the N-(3-chlorobenzyl)-2-(5-(4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl)-N-methylacetamide (0.11mmol, 44mg, 57%) as a yellow oil.

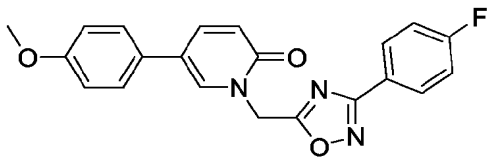
LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 4.06min; MS *m/z* (CI) $[MH]^+$= 397, 399; ^1H NMR (500MHz, $CDCl_3$) mixture 2:1 of isomers δ 2.79 (s, 3Hb), 3.05 (s, 3Ha), 3.77 (s, 3Ha, 3Hb), 4.54 (s, 2Ha), 4.70 (s, 2Hb), 4.93 (s, 2Hb), 4.93 (s, 2Ha), 6.47 (d, J=9.5Hz, 1Hb), 6.49 (d, J=9.5Hz, 1Ha), 7.00 (d, J=8.5Hz, 2Ha, 2Hb), 7.23 (d, J=7.6Hz, 1Ha), 7.30-7.35 (m, 2Ha, 2Hb), 7.35-7.41 (m, 1Ha, 2Hb), 7.41-7.51 (m, 2Ha, 2Hb), 7.82 (dd, J=2.8Hz and 9.5Hz, 1Ha, 1Hb), 7.96 (d, J=2.5Hz, 1Ha), 7.98 (d, J=2.5Hz, 1Hb).

EXAMPLE 15 : 1-((5-Fluorobenzo[*d*]oxazol-2-yl)methyl)-5-(4-methoxyphenyl)-pyridin-2(1*H*)-one (Final Compound 4-51)



According to Scheme 10 Method A: A solution of PPh_3 (3eq, 1.04mmol, 0.27g) in 1:1 acetonitrile/pyridine (3mL) was added dropwise over a period of 1 hour to a mixture of 2-(5-(4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl)acetic acid (1eq, 0.35mmol, 0.09g, Example 14 Step 2), 2-amino-4-fluorophenol (1eq, 0.35mmol, 0.04g), Et_3N (3eq, 1.04mmol, 0.15mL) and CCl_4 (4eq, 1.39mmol, 0.13mL) in 1:1 mixture of acetonitrile/pyridine (3mL). The reaction mixture was stirred at room temperature for 2 days. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 and NH_4OH. The aqueous phase was extracted 3 times with CH_2Cl_2. The combined organic fractions were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 15g SiO_2) using CH_2Cl_2/AcOEt 90/10 as eluent to afford 1-((5-fluorobenzo[*d*]oxazol-2-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (0.06mmol, 0.02g, 16%) as a brown solid. M.p.:115°C; Rf = 0.21 (CH_2Cl_2/AcOEt 90/10); LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 4.06min; MS *m/z* (CI) $[MH]^+$= 351; ^1H NMR (500MHz, $CDCl_3$) δ 3.84 (s, 3H), 5.46 (s, 2H), 6.74 (d, J=9.5Hz, 1H), 6.96 (d, J=8.8Hz, 2H), 7.05-7.12 (m, 1H), 7.35 (d, J=8.8Hz, 2H), 7.40 (dd, J=8.3Hz and 2.6Hz, 1H), 7.46 (dd, J=9.1Hz and 4.2Hz, 1H), 7.58 (d, J= 2.6Hz, 1H), 7.66 (dd, J=9.5Hz and 2.6Hz, 1H).

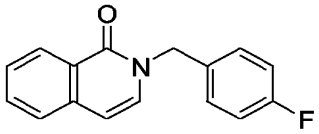
EXAMPLE 16 : 1-((3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (Final Compound 4-42)



According to Scheme 10 Method B: A mixture of 2-(5-(4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl)acetic acid (1eq, 0.23mmol, 60mg, Example 14 Step 2), 4-fluorophenylamidoxime (1.2eq, 0.28mmol, 43mg), 1-hydroxybenzotriazole (1eq, 0.23mmol, 35mg), EDCI.HCl (1.5eq, 0.35mmol, 67mg) in dioxane (2mL) was stirred at room temperature for 12 hours, then heated at 100°C for 3 days. The solution was poured onto brine and AcOEt and the aqueous phase was extracted twice with AcOEt. The combined organic fractions were washed once with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 15g SiO_2) using CH_2Cl_2/AcOEt 90/10 as eluent to afford the title compound (0.12mmol, 44mg, 50%) as a yellow solid.

M.p.: 123°C; Rf = 0.25 (CH_2Cl_2/AcOEt 90/10); LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 4.39min; MS *m/z* (CI) $[MH]^+$= 378; ^1H NMR (500MHz, $CDCl_3$) δ 3.85 (s, 3H), 5.46 (s, 2H), 6.73 (d, J=9.5Hz, 1H), 6.98 (d, J=8.8Hz, 2H), 7.13-7.18 (m, 2H), 7.36 (d, J=8.8Hz, 2H), 7.53 (d, J=2.3Hz, 1H), 7.68 (dd, J=9.5Hz and 2.3Hz, 1H), 8.05-8.08 (m, 2H).

EXAMPLE 17 : 2-(4-Fluorobenzyl)isoquinolin-1(2*H*)-one (Final Compound 13-01)

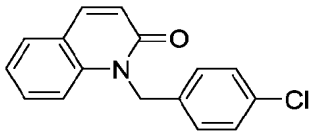


According to Scheme 11: To a solution of NaHMDS (2eq, 3.00mmol, 0.50g) in THF (3mL) at 0°C was added isoquinolin-1(2*H*)-one (1eq, 1.00mmol, 0.20g) dissolved in THF (3mL) and DMF (5mL). The reaction mixture was stirred for 10 min at 0°C then cooled at -70°C. The 1-(bromomethyl)-4-fluorobenzene (4eq, 4.00mmol, 0.80g) was added in one portion to the reaction mixture. The reaction mixture was allowed to warm to room

temperature, for one hour. Upon completion the reaction mixture was concentrated under vacuum and the crude residue partitioned between water and AcOEt, the aqueous layer was extracted with AcOEt. The combined organic layers were successively washed with water (2*30mL), HCl (1M, 2*30mL), brine (2*20mL), dried over Na_2SO_4, filtered and evaporated to afford a yellow oil. The crude compound was purified on silica gel using cyclohexane/AcOEt 80/20 as eluent to afford 2-(4-fluorobenzyl)isoquinolin-1(2*H*)-one as a white solid (0.70mmol, 0.26g, 74%).

M.p.: 107°C; LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 3.76 min; MS *m/z* (CI) $[MH]^+$= 254; ^1H NMR (DMSO-d^6) δ 5.16 (s, 2H), 6.67 (d, J=7.2Hz, 1H), 7.14-7.18 (m, 2H), 7.37-7.39 (m, 2H), 7.51 (m, 1H), 7.60 (d, J=7.2 Hz,1H), 7.66 (m, 1H), 7.71 (m, 1H), 8.23 (m, 1H).

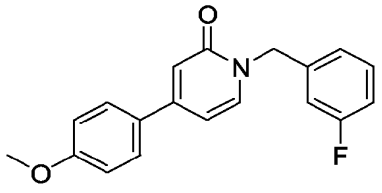
EXAMPLE 18 : 1-(4-Chlorobenzyl)quinolin-2(1*H*)-one (Final Compound 15-04)



According to Scheme 12: The title compound was prepared from quinolin-2-ol (1eq, 0.69mmol, 0.10g) and 1-(bromomethyl)-4-chlorobenzene (1.5eq, 1.03mmol, 0.21g) according to the procedure described for Example 1, Step 2. Reaction conditions: 17 hours under reflux. The residue was purified by flash chromatography on silica gel using pure CH_2Cl_2 as eluent to afford 1-(4-chlorobenzyl)quinolin-2(1*H*)-one as a white solid (0.55mmol, 0.15g, 79%).

M.p.: 139°C; LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 4.40 min; MS *m/z* (CI) $[MH]^+$= 270, 272. ^1H NMR (300MHz, $CDCl_3$) δ 5.52 (s, 2H), 6.80 (d, J=9.5Hz, 1H), 7.13-7.24 (4H), 7.25-7.30 (m, 2H), 7.40-7.48 (m, 1H), 7.58 (dd, J=1.5Hz and 7.9Hz, 1H), 7.75 (d, J=9.5Hz, 1H).

EXAMPLE 19 : 1-(3-Fluorobenzyl)-4-(4-methoxyphenyl)pyridin-2(1*H*)-one (Final Compound 11-03)



Step 1 : 1-(3-Fluorobenzyl)-4-(3-fluorobenzyloxy)pyridin-2(1H)-one

According to Scheme 13 Step 1: The title compound was prepared from pyridine-2,4-diol (1eq, 2.52mmol, 0.28g) and 1-(bromomethyl)-3-fluorobenzene (3eq, 7.56mmol, 0.93mL) according to the procedure described for Example 1 Step 2. Reaction conditions: 17h under reflux in DMF. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/AcOEt 90/10) to afford 1-(3-fluorobenzyl)-4-(3-fluorobenzyloxy)pyridin-2(1*H*)-one as a white solid (0.95mmol, 0.29g, 36%).

M.p.: 121°C; LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 4.33 min; MS *m/z* (CI) $[MH]^+$= 328; ^1H NMR (DMSO-d^6) δ 7.72 (d, 1H, J=7.88 Hz); 7.47-7.42 (m,1H); 7.40-7.38 (m, 1H); 7.28-7.26 (m, 2H); 7.18 (m, 1H); 7.10-7.07 (m, 3H); 6.08-6.06 (dd, 1H, J=2.8 Hz, J=7.56Hz); 5.93(d, 1H, J=2.83Hz); 5.09(s, 2H); 5.02 (s, 2H).

Step 2 : 1-(3-Fluorobenzyl)-4-hydroxypyridin-2(1H)-one

According to Scheme 13 Step 2: A suspension of 1-(3-fluorobenzyl)-4-(3-fluorobenzyloxy)pyridin-2(1*H*)-one (1eq, 0.95mmol, 0.29g) and Pd/C (0.3eq, 0.29mmol, 30.3mg) in MeOH (3mL) was hydrogenated until complete (30 min). The suspension was filtered through celite and the filtrate concentrated under vacuum to afford 1-(3-fluorobenzyl)-4-hydroxypyridin-2(1*H*)-one (0.75mmol, 0.16g, 79%) as a white powder.

LC (XTerra RP_{18}, 3.5µm, 3.0x50mm Column): RT = 2.88 min; MS *m/z* (CI) $[MH]^+$= 220.

Step 3 : 1-(3-Fluorobenzyl)-1,2-dihydro-2-oxopyridin-4-yl trifluoromethanesulfonate

According to Scheme 13 Method B: To a solution of 1-(3-fluorobenzyl)-4-hydroxypyridin-2(1*H*)-one (1eq, 1.00mmol, 0.30g) and pyridine (3eq, 4.00mmol,